STUDY ON PREVALENCE AND CORRELATION OF LIVER FUNCTION ABNORMALITIES IN HEART FAILURE PATIENTS IN TIRUNELVELI MEDICAL COLLEGE HOSPITAL

Dissertation submitted to

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

in partial fulfillment for the Degree of

DOCTOR OF MEDICINE - BRANCH I GENERAL MEDICINE

MAY 2018

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

TIRUNELVELI - 11, TAMIL NADU

CERTIFICATE

This is to certify that the dissertation entitled **" STUDY ON PREVALENCE AND CORRELATION OF LIVER FUNCTION ABNORMALITIES IN HEART FAILURE PATIENTS"** submitted by Dr.M.KARTHIKA to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the award of M.D. Degree (GENERAL MEDICINE) is a bonafide work carried out by her under my guidance and supervision during the course of study 2015-2018. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other.

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DECLARATION

I solemnly declare that the dissertation titled "**STUDY ON PREVALENCE AND CORRELATION OF LIVER FUNCTION ABNORMALITIES IN HEART FAILURE PATIENTS**" is prepared by me.

The dissertation is submitted to **THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY** towards the partial fulfillment of requirements for the award of M.D. Degree (Branch I) in General Medicine. I also solemnly declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any university, found either in India or abroad.

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Last but not the least, I thank **almighty god**, for giving me wisdom, favours and blessing.

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PRINCIPAL INVESTIGATOR: Dr. M. KARTHIKA, MBBS

DESIGNATION OF PRINCIPAL INVESTIGATOR: POST GRADUATE IN GENRAL MEDICINE

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Dear , Dr. Karthika, MBBS.,, The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 05.08.2016.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1. TIREC Application Form ☐
2. Study Protocol ☐
3. Department Research Committee Approval ☐
4. Patient Information Document and Consent Form in English and Vernacular Language ☐
5. Investigator's Brochure ☐
6. Proposed Methods for Patient Accrual Proposed ☐
7. Curriculum Vitae of the Principal Investigator ☐
8. Insurance /Compensation Policy ☐
9. Investigator's Agreement with Sponsor ☐
10. Investigator's Undertaking ☐
11. DCGI/DGFT approval ☐
12. Clinical Trial Agreement (CTA) ☐
13. Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA) ☐
14. Clinical Trials Registry-India (CTRI) Registration ☐

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1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
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CERTIFICATE - II

This is certify that this dissertation work title **"STUDY ON PREVALENCE AND CORRELATION OF LIVER FUNCTION ABNORMALITIES IN HEART FAILURE PATIENTS"** of the candidate **Dr.M.KARTHIKA** with registration Number **201511355** for the award of M.D. in the branch of **GENERAL MEDICINE.** I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion page and result shows **1 percentage** of plagiarism in the dissertation.

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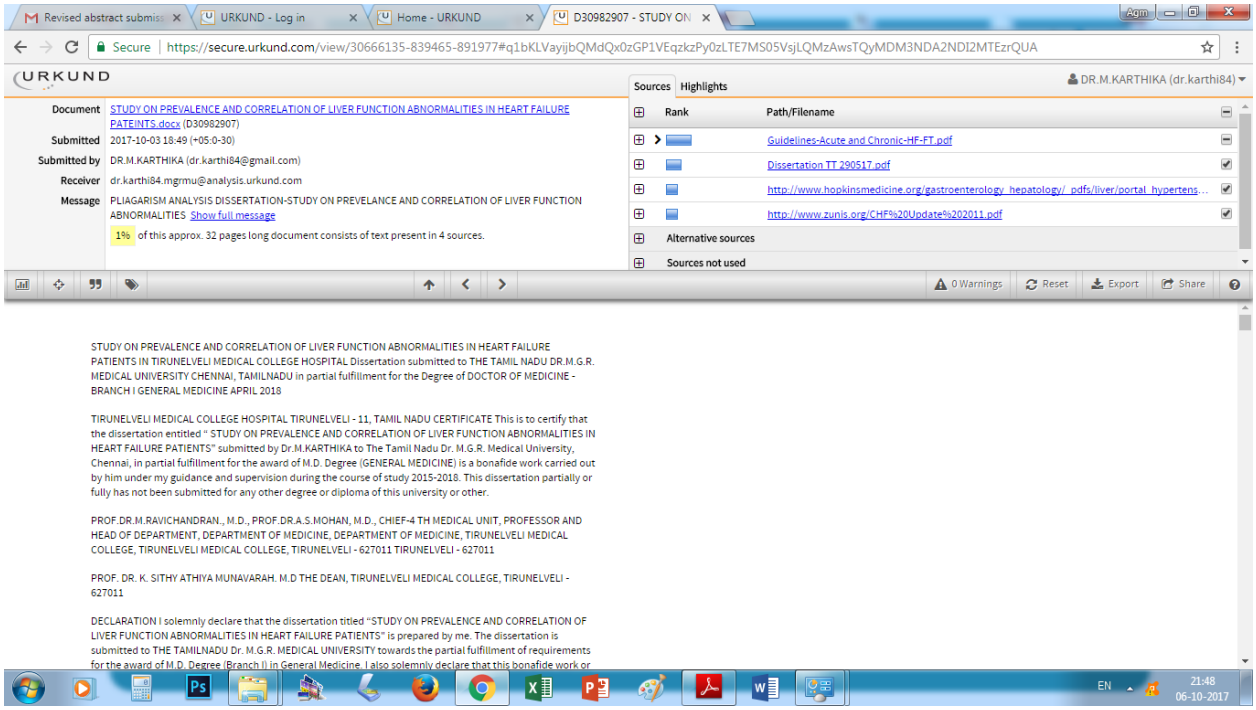
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CONTENTS

INTRODUCTION

The clinical syndrome of heart failure encompasses many clinical features that negatively affects almost all the vital organs in the body. These features can be due to both systolic failure as well as the diastolic feature whose nomenclature has undergone recent modifications as that heart failure with reduced ejection fraction and heart failure with preserved ejection fraction respectively. Even though there many studies regarding the affection of renal system in cases of heart failure ,the liver with its dual supply bears the brunt of both types of heart failure leading onto derangement of its functions. The liver is a multi faceted organ with high level of metabolic functions and hence is highly dependent on hepato-cardiac vascular connections, both arterial supply to provide high oxygen supply and venous drainage to remove the catabolic waste products. As a result of the hepatic dysfunction, there occurs many of biochemical alterations in the liver function tests that are usually measured in patients admitted for treatment. These abnormalities not only bare open the effects of heart failure over liver but may also help in the assessing the severity of the failure as well prognostication of the acute as well as the chronic heart failure patients. Hence the study on effects of both types of heart failure on the liver becomes more important in the evolving scenario of cardiac morbidity and mortality.

This study is based on the need for assessing prevalence of liver dysfunction and its implications correlating the biochemical

alterations of liver function with the severity of heart failure patients in the Tirunelveli Medical College. With a start up study of this kind, the emerging use of liver function test for assessing and obtaining the severity of heart failure patients without major invasive and expensive investigations can be considered . It can also be extrapolated to use in primary care and secondary care settings in the state of Tamilnadu which is one of leading state in healthcare in India.

AIMS OF THE STUDY

AIMS OF THE STUDY

1.To study prevalence of liver function abnormalities in heart failure patients using liver function tests.

2. To correlate the liver function tests abnormalities with Clinical,Biochemical and Radiological severity of heart failure patients.

REVIEW OF LITERATURE

HEART FAILURE

Heart failure syndrome produces great deal of great morbidity and mortality overload on the health systems of developed and developing countries in terms of health, economic and social aspects. The population that is affected by heart failure is growing exponentially with that of aging of social demography, improved treatment and survival after myocardial infarction and also prevention of sudden cardiac death to an extent [(2)]. Heart failure syndromes can be classified as :

1) Acute heart failure
2) Chronic heart failure

The recent classification of heart failure focuses upon the function of the left ventricular system and hence they are now classified as :

1) Heart failure with reduced ejection fraction (EF <40%)
2) Heart failure with preserved ejection fraction(EF >40%)

ETIOLOGY:

Heart failure with reduced ejection fraction [(1)] :

1) coronary artery disease
2) chronic volume overload- regurgitant lesions, intra and extra cardiac shunting
3) chronic pressure overload- hypertension , obstructive lesions
4) chronic lung disease- cor pulmonale , pulmonary vascular disorders

5) non ischemic dilated cardiomyopathy- infiltrative, familial

6) toxic / drug induced

7) infections –viral, Chagas disease

8) rate and rhythm disorders- chronic bradyarrythmias and chronic tachyarrythmias

Heart failure with preserved ejection fraction [1] :

1) hypertrophy –hypertrophic cardiomyopathy, hypertension

2) age

3) restrictive cardiomyopathy- amyloidosis, sarcoidosis, hemochromatosis

4) fibrosis

5) obesity

6) endomyocardial disorders

High output states [1] :

1) thyrotoxicosis

2) nutritional disorders- beriberi

3) chronic anemia

4) systemic arterio-venous shunting

PATHOPHYSIOLOGY OF HEART FAILURE [3]:

Heart failure is a complex clinical syndrome that can defined in terms of dysfunction that is associated with structural as well as functional compromise of myocardium resulting in typical symptoms of breathlessness and easy fatiguability. The models that described heart failure such as ‘cardiorenal model’ endorsing the effects of excessive salt and water retention or the ‘cardiocirculatory’ model emphasizing the abnormality in the pumping mechanism of heart with its output capacity are not well accepted. The main baseline of heart failure is the impaired ability of myocardial pump to act as an effective pump maintaining the circulation and perfusion of the bodily systems. The different set of adjustments and acclimatizations that occur in the setting of the heart failure decide and contribute to the progressive long term morbidity and mortality of heart failure patients.

Acute events like myocardial infarctions, myocarditis or events with slow onset such as acquired cardiomyopathies, hypertensive heart disease, valvular heart disease and genetic cardiomyopathies will all lead to the decline in the pumping capacity or filling capacity affecting the systolic and diastolic functions respectively. This signifies the variable nature of the symptoms that would be associated with heart failure varying from being asymptomatic to severe dyspnoea, fatigue and mortality. These symptoms associated not only are dependent on the onset but also the effects of the compensatory mechanisms that get activated once heart failure propagates and

sustains itself in long term. The specific pathology that lies central any heart failure which is the 'Left Ventricular remodeling' occurs with the sustained activation of the neurohormonal system . This type of remodeling could possibly by itself lead onto the progression of heart failure and can affect the ejection fraction of left ventricle .

The mechanism behind the model heart failure are [3] :

1) Neurohormonal mechanisms-

2) Left ventricular remodeling

Neurohormonal mechanisms:

Eventhough the term 'neurohormonal' signifies the original thought of molecules that were produced in the neuroendocrine system , recent concepts suggest that all those molecules like nor epinephrine (NE) and angiotensin 2(AG2) are produced in the myocardial fibres itself and act as paracrine or autocrine manner creating a unitary concept of ' neurohormonal theory'.

Symphathetic system activation :- During the early course of heart failure , the symphathetic system starts to get stimulated with the concominant suppression of the parasymphathetic system in the body due to the inhibitory inputs received from the baroreceptors such as carotid and aortic barreceptors but also due to the increase in the excitatory inputs from the metaboreceptors and peripheral

chemoreceptors [6]. The net result due to this activation is the loss of normally occurring heart beat variability as well as increased peripheral resistance with the increase in the symphathetic stimulation. There is also increase in the nor-epinephrine discharge and concentration in the circulating blood. This increase in norepinephrine levels are not sustained in the long term due the exhaustion of the cardiac reserves in the myocardial interstium and also the down regulation of enzyme complex of tyrosine hydroxylase which is needed for norepinephrine production.

Due to the elevated levels of symphathetic activation molecules in the body , the beta adrenergic receptor activation leads to increase in heart rate and also the force of contraction while the alpha adrenergic activity increase to produce the dominant effect of peripheral vasoconstriction. It is clear from this points that the symphathetic system overdrive helps in the short trem compensation of effects of the pump failure in heart failure patients while in long term these effects can lead onto the maladaptive processes taking over to produce left ventricular dysfunction either in terms of systolic or diastolic dysfunction. Two large ongoing trials such as INNOVATE HF and NECTAR HF are examining the effects of vagal nerve stimulation on the left ventricular structure and the clinical outcomes in New York Heart Association (NYHA) class 3 failure patients.

Renin Angiotensin aldosterone system: (RAAS)

RAAS is activated only in the later stage of heart failure unlike the symphathetic system [6] . This activation of RAAS can be due to either the associated hypoperfusion of the renal vasculature or the decrease in the filtered load of sodium reaching the sensing organs of macula densa situated in the distal nephron along with concomitant increase in the activity of symphathetic system leading onto activation of RAAS and secretion of the renin in the blood. The logical final step in RAAS activation is the production on Angiotensin 2 (AG2) which is by far the most potent major vasoconstrictor substance . The production of AG2 can occur through two pathways :

1) Angiotensin converting enzyme (ACE) dependent pathway
2) Angiotensin converting enzyme (ACE) independent pathway

ACE dependent pathway occurs 90% in the peripheral tissues while the remaining 10% occurs in the heart and its blood vessels, while the ACE independent pathways are through the activation of chymase, kallikrein and cathepsin G pathways leading onto to the fact that ACE inhibitors alone cannot lead onto complete suppression of the Angiotensin production having major implications in the treatment of heart failure. Angiotensin (AG2) exerts its effect mainly through two receptors ,namely, angiotensin receptor 1(AT1) and receptor 2(AT2). The first receptor is

predominantly seen with the vascular channels of our body while that the AT 2 receptor are mainly seen the heart muscles and the fibroblasts within it. In the later stages of the heart failure , the AT1/AT2 receptor ratio is decreased leading onto the vasodilatation, natriuresis and the increased secretion vasodilators such as bradykinin .[6]

The sustained elevation of AT 2 receptors will lead onto maladaptive changes in the heart in the long term effect producing fibrosis and enhanced secretion of norepinephrine along with aldosterone secretion due to stimulation of zona glomerulosa [5] . This effect of increased aldosterone may aid in the excretion of potassium while that of fibrosis and decreased ventricular compliance and increased stiffness due to fibrosis. The importance of aldosterone lies in the fact that in addition to sodium retention , it can also provoke endothelial dysfunction, baroreceptor dysfunction and inhibition of norepinephrine release along with increased oxidative stress.

Oxidative free radicals are formed as result of metabolic activity exceeding the ability of the body systems to scavenge them properly . The increase in production of oxygen radicals that cause severe metabolic stress on the failing myocardium are due to mechanical strain imposed , neurohormonal stimulation and elaboration of the inflammatory cytokines. Aldosterone antagonists play an important role in prevention of

morbidity and decreased hospitalizations of heart failure patients which have been confirmed in many trials .

Alterations in renal functions:

These alterations that occur in renal system and its function are primarily due to the decrease in the effective intravascular volume leading onto to decreased filling of the ventricles inspite of the patient being in volume overload condition where the fluids accumulate in the interstitial space. This process of alterations occur mainly due to the decrease in effective cardiac output rather than "forward failure" model suggesting increased sodium reabsorption due to renal hypoperfusion or the "backward failure" model suggesting the increased transudation of salt and water from the intravascular space to the extravascular compartment [(2)]. These impulses cause baroreceptor mechanisms to get activated thereby causing sustained symphathetic stimulation. The profound effects of volume overload occurring with renal dysfunction is coupled with the release of arginine vasopressin (AVP) which contributes to decreased water as well as solute excretion. Circulating AVP are seen in greater amounts in heart failure patients which may cause hyponatremia (even after the blood osmolality is corrected) [(7)] .

The effects of symphathetic stimulation, RAAS activation and AVP over secretion can be blunted by the counter regulatory vasopeptides comprising of prostaglandins, atrial natriuretic paptide (ANP),

brain natriuretic peptide(BNP) . Natriuretic peptides are released in response to the activation of the stretch receptors in the myocardium . These peptides offset the effects of the neurohormonal affects previously described causing progression in heart failure Natriuretic peptides are of five types: ANP -Atrial natriuretic peptide, BNP- Brain natriuretic peptide, CNP, DNP, Urodilantin [6].

These natriuretic peptides act on different receptors, namely, A receptor(ANP & BNP), B receptor (only by CNP) which are coupled to the guanylcyclases resulting in natriuresis, inhibition of fibrogenic stimuli and vasorelaxation occurring due to decreased RAAS stimulation. The other receptor is of C type is for the degradation of the natriuretic peptides which are cleared by the neutral endopeptidases, otherwise called as nephrilysin. The use of aldosterone antagonists, nephrilysin inhibition had produced good results showing great impact on the left ventricular structure and function in patients with heart failure with preserved ejection fraction. [7]

Alterations in peripheral vasculature:- In patients suffering from chronic heart failure , the interacting autonomic and local autoregulatory mechanisms preserve the circulation of essential organs like brain and heart while decreasing the blood supply to visceral organs and gut. During exercise, there is increase demand of blood from the skeletal muscles in already decompensated patients, there is potential stimulation of symphathetic system which leads onto peripheral vasoconstriction. There are many vasoconstrictors in play in this

process which includes norepinephrine, endothelin, urotensin, neuropeptide Y , thrombaxane A2 and AVP.

Left Ventricular Remodelling:

Even though the neurohormonal model of heart failure lays emphasis on the stabilization and certain reversibility in the process of heart failure , the truth is that this process once started will definitely progress at one rate or another . Many published review have shown that the process of Left ventricular remodeling has a direct bearing on the left ventricular performance and thereby the deterioration of left ventricle including the progression of heart failure.

The left ventricular remodeling has been traditionally discussed in terms alteration in the cardiac myocyte, changes in the volume of myocyte and non myocyte cells, geometry and architecture of the LV.

The pattern of cardiac hypertrophy occurs in two basic patterns. They are:

Concentric hypertrophy [3]:- In case like aortic stenosis or hypertension ,the systolic wall stress increases result in addition of sarcomeres in parallel ,an increase in the cross sectional area and increased left ventricle thickening . This concentric hypertrophy has been linked with alteration in calcium/calmodulin dependent protein kinase 3 dependent pathway.

Eccentric hypertrophy [3] :- In case of regurgitant lesions like mitral and aortic insufficiency , increase in the diastolic wall stress leads to increase in myocyte length as well as addition of myocyte in series producing left ventricular enlargement which has been linked to AKT pathway. The myocyte arrangement occurs in heart failure cases has elongated morphology with or without left ventricle wall thickening.

The normally elliptical chamber cross section of the left ventricle will turn into a spherical chamber after left ventricle remodeling producing additive meridional stress on the walls of myocardial pump. This load that is excessively produced is transferred onto the ventricles both during the systole as well as diastole thereby increasing the energy expenditure of the myocardium. The proportionate left ventricle wall thinning occurs with the increasing end diastolic pressure and volume. This leads onto the functional afterload mismatch on the the heart producing further decrease in the cardiac output. This stress will cause increase secretion of stretch receptor activated vasopeptides pathways and hypertrophic pathways. These changes cause episodic hypoperfusion of the subendocardial myocytes, increased amount of oxidative stress and increased free radical injury. The most serious and important mechanical complication is the pulling apart of the papillary muscles leading onto “functional mitral insufficiency”.

Most the the medical and device assisted therapy lead onto decrease in left ventricular mass and volume restoring the ventricle to its original mass and size , a process known as ‘reverse ventricular remodeling’or ‘myocardial recovery’ [3]. Myocardial remission refers to normalization of morphologic changes even when there are factors provoking heart failure while myocardial recovery signifies normalization with freedom from subsequent heart failures.

Clinical features :

Symptoms:

1) fatigue- it is mainly related to low cardiac output, anemia and skeletal muscle abnormalities

2) dyspnoea – it is multifactorial in origin and occurs due to stimulation of sensors such as stretch receptors, metaboreceptors and juxta capillary J receptors which results in shallow breathing , typical of cardiac origin.

3) orthopnoea - Dyspnoea that occurs in recumbent position due to fluid shift into the intravascular compartment from interstitial space which gets relieved with sitting upright.

4)PND- Paroxysmal Nocturnal dyspnoea refers acute episode of dyspnoea and coughing usually 1-3 hrs awakening the patient from bed

5) Nocturnal cough, oliguria, nocturia, insomnia

6)Abdominal distension due to fluid collection, right upper quadrant pain due to stretching of liver capsule and dependent edema.

Signs:

1) reduction in blood pressure, tachycardia, narrowing of pulse pressure

2) laboured breathing, cyanosis

3) elevated jugular venous pressure, giant ‘v’ waves in tricuspid regurgitation

4)pulmonary crackles, expiratory wheeze, pleural effusions

5) Tender hepatomegaly, jaundice, ascites and peripheral edema

6) Displaced apical impulse, third heart sound, fourth heart sound (diastolic failure)

Criteria used to diagnose heart failure – Framingham heart study, NHANES criteria

Framingham Criteria

MAJOR CRITERIA	MINOR CRITERIA	MAJOR OR MINOR CRITERIA
Paroxysmal nocturnal dyspnea or orthopnea	Ankle edema	Weight loss > 4.5 kg in 5 days in response to treatment
Neck-vein distention	Night cough	
Rales	Dyspnea on exertion	
Cardiomegaly	Hepatomegaly	
Acute pulmonary edema	Pleural effusion	
S3 gallop	Vital capacity decreased by one third from maximal capacity	
Increased venous pressure > 16 cm H_2O	Tachycardia (rate > 120 beats/min)	
Hepatojugular reflux		

NHANES Criteria		
CATEGORY	**CRITERION**	**SCORE**
History	Dyspnea	
	When hurrying on a hill	1
	When walking at an ordinary pace	1
	Do you stop for breath when walking at an ordinary pace?	2
	Do you stop for breath when walking after 100 yards on flat ground?	2
Physical examination	Heart rate	
	91-110 beats/min	1
	>110 beats/min	2
	Jugular venous pressure > 6 cm H_2O	
	Alone	1
	PLUS hepatomegaly or edema	2
	Rales	
	Basilar rales	1
	Rales of more extensive distribution (beyond basilar)	2
Chest radiography	Upper zone flow redistribution	1
	Interstitial pulmonary edema	2
	Interstitial edema plus pleural fluid	3
	Alveolar fluid PLUS pleural fluid	3

Criteria: 2 major criteria or 1 major criterion in conjunction with 2 minor criteria in Framingham study and 3 points in NHANES study

LABORATORY TESTS :

1) Routine blood tests such as complete hemogram , panel of electrolytes , renal and liver function tests, serum uric acid, assessment for diabetes, dyslipidemia and thyroid functions are to be done.

2) Electrocardiogram reveals the rate, rhythm , chamber enlargement, evidence of previous ischemia and also to look for QRS length to decide the patient for cardiac resynchronization.

3) Chest X-ray says about the cardiac size, shape and pulmonary edema if any.

4) Assessment of LV function is done through the non invasive means like echocardiography/Doppler as well as Magnetic resonance imaging by which ejection fraction as a measure of contractility ac be assessed along with right ventricular and pulmonary vasculature changes , tissue & pulse wave Doppler to assess diastolic dysfunction .

5) Bio markers such as B Type Natriuretic Peptide (BNP) , N-terminal Pro BNP , galectin and soluble ST-2 protein have been measured ,correlated well with the incidence as well as the severity of heart failure and are helpful with optimizing the dosage in relation to varying levels of the markers.

6) Exercise testing is done rarely and useful to assess the need for cardiac transplantation if the peak oxygen uptake of <14 ml/kg which is usually associated with poor prognosis.

Management of heart failure:

1**) Acute decompensated disease [3] :**

General measures:

*) Identifying the problem and evaluation regarding nonadherence of medications, cardiac stimulant usage, active infections, thrombo embolisms ,arrhythmias which tend to precipitate heart failures should be done and assessment done accordingly.

*) A parallel step is to stabilize the patient's hemodynamic status.

Specific measures :

*) Volume management :

Diuretics remain the mainstay of volume balance in these patients with usage of thiazides like metazolone in combination with loop diuretics like frusemide having synergistic effect and they can be given either as high dosage regimen or continuous infusion when there is poor oral absorption and need for rapid relief . They are continued till the patient achieves euvolemia. In late stages of heart failure reduced use of diuretics and continued inotropic support have helped to maintain the renal perfusion , thereby preventing cardiorenal syndrome progression.the use of ultrafiltration in refractory cases have the potential advantages such as neutral effect on serum electrolytes , controlled fluid removal and decreased neurohormonal activity. Cardio Renal Rescue Study in Acute Decompensated Heart Failure (CARESS –HF) trial shows no mortality benefits from ultrafiltration when compared to conventional pharmacotherapy.

*) Vascular Therapy:

Use of intravenous nitrates, nitroprusside and nesiritide are considered with nesiritide showing increased incidence of renal dysfunction and hypotensive episodes. Serelaxin or human recombinant human relaxin -2 has

been used to improve dyspnoea, symptoms of congestion and less worsening of heart failure.

*) Inotropic support :

Milrinone and dobutamine are the commonly used inotropes in the setting of low output cardiac failure cases which relieve the congestion rapidly by virtue of their action on myocardial contractility . Milrinone score s over dobutamine since it acts downstream on beta receptors hence used in patients on beta blocker therapy. Novel inotropes such as levosimendan and Omecamtiv are being considered due to their action on myofilament sensitization rather then increasing calcium concentration in myofibrils [7].

2)Heart failure with reduced ejection fraction :

Renocentric (diuretics) and hemodynamic models (digoxin and inotropes) have been replaced with the neurohormonal models involving ACEI(Angiotensin Converting Enzyme Inhibitors) and beta blockers leading onto increased improvement in cardiac structure with relief of symptoms.

Neurohormonal antagonism :

ACEI s, ARBs (Angiotensin Receptor Blocker) and beta blocker therapy have decreased both morbidity and mortality of heart failure patients even in advanced states [7] . While these effects are seen as a class effect in ACEIs , beta blockers efficiency is limited to specific drugs like bucindolol and xamoterol which have intrinsic sympathomimetic activity. Both these drugs have dose dependent decrease in morbidity and hospitalizations

helping in easy titration every two weeks. ARBs have the potential to neutralize the “Aldosterone Escape “ that occurs with chronic ACEIs therapy [6].

Mineralocorticoid antagonists like spironolactone and selective drugs like eplerenone have again reduced hospitalizations in symptomatic NYHA III & IV class patients . Hyperkalemia and worsening renal functions are main impediments to upward titration of these drugs .

Arteriovenous vasodilators :

Drugs such as hydralazine and nitrates by producing systemic vasodilatation have helped in improving the failure symptoms to an extent in patients who are not tolerant to neurohormonal blockade due to worsening renal functions and hyperkalemia.

Inotropes :

Digitalis glycoside exert mild inotropic and symphatho- inhibitory effects and attenuate the carotid baroreceptor reflexes decreasing serum rennin and aldosterone levels. Low doses of digoxin are sufficient to produce beneficial effects while higher doses are associated with potential mortality risks.

Others :

Ivabradine is a inhibitor of cardiac I_f current in the sinoatrial node leading onto slowing of heart rate with no negative inotropic effect. Diuretics are needed at the outset to correct hypervolemia before the

neurohormonal therapy sets in . Newer calcium channel inhibitors like amlodipine and felodipine have morbidity benefits while statins and anticoagulants have not demonstrated potential benefits . Micronutrients like fish oil with long chain omega unsaturated fatty acids and thiamine in chronic heart failure patients have led to improved outcomes and reduced hospitalizations .

Enhanced External Counterpulsation (EECP) using graded external pneumatic compression of peripheral lower extremities which is administered in 1 hour sessions for 35 treatment days has been proposed to reduce symptoms as well as exercise induced ischemia .Cardiac Resynchronization Therapy helps in more synchronous ventricular contraction and done as the last resort in refractory heart failure patients and its efficiency has been demonstrated in CARE –HF (Cardiac Resynchronization in Heart Failure Study). Enzyme replacements and gene therapy are evolving concepts which are impotents in related conditions.

3)Heart failure with preserved ejection fraction :

Therapeutic end points in HFpEF patients are to relieve congestion, stabilization of blood pressure , control of heart rate and improving exercise tolerance. Various trials like CHARM and I-PRESERVE involving ARBs did not yield greater benefits. Novel therapy like sildenafil have proved less beneficial but an hybridized molecule of ARB with an endopeptidase inhibitor , LCZ696, enhances myocardial relaxation and

reduction in ventricular hypertrophy promising future evaluations and potential use in these subsets of patients.

THE LIVER :

The liver is an important solid organ in the abdomen with variety of functions which include the synthetic, digestive, detoxifying, maintaining blood hemostasis , storing of blood as well as micronutrients etc. In the adult life though the liver receives blood supply from that the portal vein comprising of more than 80% and the remaining 20% from the systemic circulation ,namely, the hepatic artery and drained by hepatic veins into the systemic circulation. The portal vein is formed by the joining of the splenic vein draining the spleen and greater curvature of the stomach with that of the superior mesenteric artery which drains the small intestine and colon . The hepatic artery arises from the celiac trunk dividing into the right and left artery while sending of a cystic artery branch also. The hepatic veins are usually 3 in number while there can be many anatomical variation noticed in more than 30% of individuals.

The portal flow is interconnected with the systemic circulation because the draining of blood from gut which consists of the nutrients that were absorbed is mainly due to blood supply from the systemic arteries . Since there are connections between portal and systemic circulation in the areas like paraumblical, bare area of liver ,retroperitoneal, rectal and lower

end of esophagus there always exists a bypass for portal blood to enter into the systemic circulation without involving the liver. The hepatic excretion of bile is through the biliary system which comprises of intra as well as extrahepatic ducts with the cystic duct where the bile drains ultimately into the second part of duodenum. The hepatic microanatomy consists of the sinusoids arranged in pentagonal patterns within the liver with the central vein and portal triads. Rappaport classification details about 3 zones of hepatic acini [5]:

Zone 1: around the portal triad, where the nutrient and oxygen content is more due to mixing of blood in sinusoids

Zone 2: the middle zone

Zone 3: the most prone area foe ischemia surrounding the central vein and hence important in hypoperfusion injuries.

The arterial flow is inversely related to portal flow probably due to the mechanism of hepatic arterial buffer response based on washout of locally produced adenosine. This molecule adenosine secretion and concentration is influenced by hepatic lobular blood flow acting by release of nitrous acid and also experimental models have shown that infusion of adenosine have reduced ischemic liver injuries.

CIRCULATION AND LIVER [4]:

The response to circulatory dysfunction , be it congestive or ischemic ,there occurs typical histological and biochemical abnormalities. When the ischemic state do affect the liver cells it is more so in the zone 3 perivenular region which resolves spontaneously when there is reperfusion. The biochemical changes occur in form of drastic and enormous elevation of the hepatic liver enzymes, namely, AST and ALT along with increase in serum bilirubin also. These abnormalities can depend upon the time duration of disease state, liver condition and the associated drug related liver toxicity. This liver dysfunction is also noticed with passive congestion whose pathophysiology and features are to be discussed below.

The main disease states that can cause defects in the hepatic circulation and thereby disease state are left and right ventricular failure ,ischemic cholangiopathy, valvular heart disease, constrictive pericarditis, heat stroke, hepatic infarction. Other processes that can affect liver biochemistry are sepsis, venous thrombosis and vasculitis etc. These effects are more pronounced with that of hepatic arterial obstruction since it supplies singularly the bile ducts, both intra as well as extrahepatic . Hepatic infarction that occurs with that of hypoperfusion results in infarction at all levels ,segmental, subsegmental and lobar.

ISCHEMIC HEPATITIS:

Ischemic hepatitis signifies deceased oxygen delivery due to systemic hypotension and also cardiac pump failure leading onto global hypoperfusion. Hepatic blood decreases to an extent of 10% when the blood pressure falls by 10 mm Hg and will not be injurious in normal persons due to compensatory mechanisms that come into play during circulatory failure.This pump failure as earlier discussed can occur due to result of myocardial infarction, congestive heart failure, massive pulmonary embolism, septic shock, heat stroke, dehydration and also hypovolemia due to massive bleed. Shock liver is specific term used when there is shock related effect.

The pathological basis behind ischemic hepatitis is different since inflammation is not a hallmark of this .The specific feature that is present is the zone 3 necrosis with a highly variable lobular collapse which could vary depending upon the the duration and the severity of the insulting process. In cases of right ventricular acute infarction, the liver histology shows features of both congestive and ischemic hepatitis characteristics. These microscopic alterations in the histology resolve spontaneously over a given period of time and then liver continues to regenerate except in persons having co morbid liver illness where the changes tend to stay or recur.

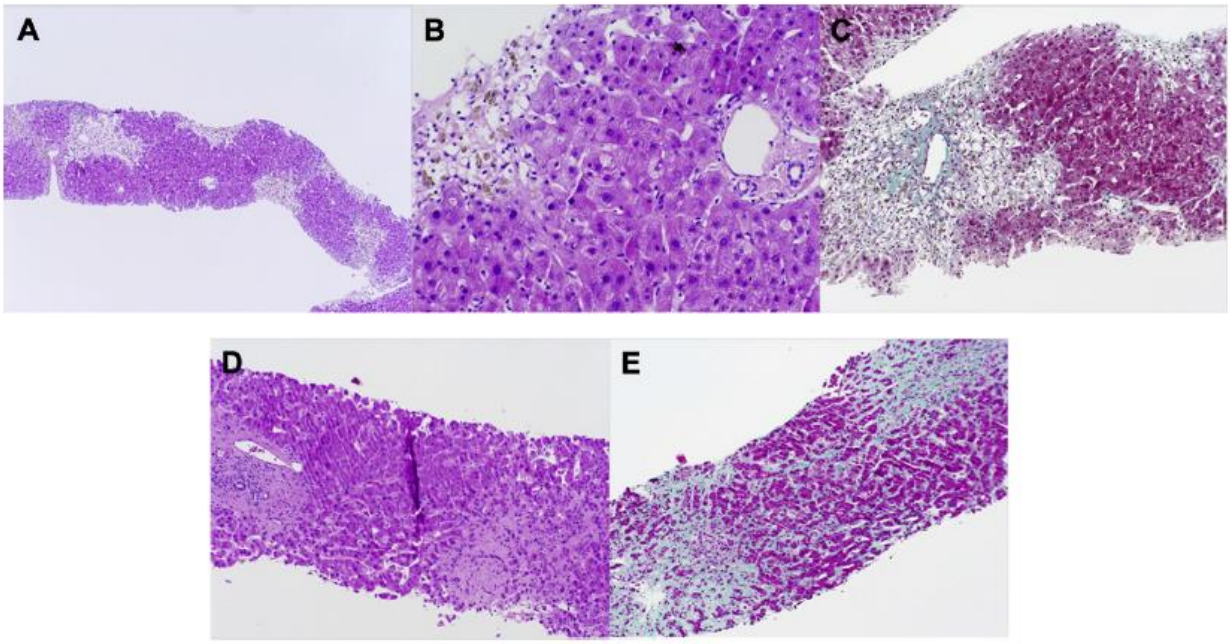
The important feature of ischemic hepatitis or acute cardiogenic liver injury (ACLI) is the enormous elevation the hepatic enzymes, namely, the aminotransferases and lactate dehydrogenase (LDH). The increase

occurs in 24 -48 hrs with the development of circulatory failure and this feature resolves in 4 to 7 days if the hypotension has been treated properly. The elevation that occurs can be in the range of 1000 IU/litre and easily picked up owing to complete screening of the acutely ill patient. The rise in LDH parallels that of alanine transaminases (ALT) and usually ALT/LDH ration is within the 1.5 range. This rise in serum transaminases also can occur in toxic as well as infectious hepatitis but can be differentiated with the speedy recovery of transaminases to normal level in ischemic hepatitis as well as clinical features of viral infections. Ischemic hepatitis is also associated with rise in renal function tests values since the same circulatory failure affects the kidneys while other causes of transaminases elevation don't see the same.

Serum bilirubin will continue to rise after the elevation of the transaminases and will peak around 3-4 days . This rise in serum bilirubin values is greatly influenced by the associated co morbid illness of the liver in particular and the hemodynamic status of the patients in general. The other tests that can be abnormal are that of Prothrombin time where the international normalized ratio (INR) can be increased mildly and also resolves with vitamin K support to the liver. The variations in serum ammonia level in ACLI is not much so as to cause encephalopathy which can other wise be caused by circulatory failure leading onto hypoxic brain damage.

The pattern of elevation in enzymes can occur with subclinical effects of hypotension which can incite the liver injury commonly seen in patients with chronic heart failure both systolic and diastolic . Seeto et al.[9] found that hypotension alone did not induce acute liver injury. Patients with ACLI were compared with a control group comprising trauma victims who had evidence of prolonged hypotension . Henrion et al. [8] examined ACLI in patients admitted to the coronary intensive care unit with evidence of low cardiac output. Patients with biochemical evidence of cardiogenic injury had significantly higher central venous pressures compared to patients who had low cardiac output but no ACLI. The cirrhotic patients developing hypotension and ischemic hepatitis have mortality in excess of 60-70% even with advanced hospital care.

The treatment of ischemic hepatitis starts with the correction of circulatory failure and reverting back to normal hemodynamics. Some trial studies have been undertaken but a set protocol or drug therapy has not been devised to treat this condition. Dopamine infusion in one study has tried in which it improved hepatic blood flow but the benefits of hepatic recovery could not be noticed . Adenosine as discussed earlier may be involved in hepatic buffering system but this drug has been utilized only in animals while in humans only to prevent reperfusion injury after live donor graft.



Histology slides:

A) changes with ACLI-original magnification *4

B) original magnification *20-Pattern of hepatocyte loss is consistent with ischemic injury. Hepatocytes have completely disappeared , leaving a loose reticular framework while there is no regenerative collagen activity

C) Masson trichrome stain, original magnification*10 thereby suggesting a fairly recent event. The presence of mild ductular changes including ductular proliferation, occasional neutrophils associated with ductules, and ductular bile stasis are likely secondary to the ischemic event

D) Changes consistent with chronic hepatic passive congestion, in a patient with chronic HF . There is minimal inflammation in the portal areas, and no interface activity is evident. Only 1 focus of canalicular cholestasis is seen. Extensive spidery and dense perivenular fibrosis

exists; this extends into the lobule and bridges (stage 3) with other central, and focally, portal areas

E) Masson trichrome stain (original magnification *10) highlights the extensive nature of zone 3 (central) fibrosis. Some of the perisinusoidal hepatic plates are atrophic and attenuate

HEPATIC INFARCTION:

This is the most severe form of hepatic ischemia wherein there is total occlusion of blood supply at level of lobar,segmental or subsegmental leading onto coagulative necrosis. The only mode of healing in this processs is through fibrosis and scar formation. The severity of hepatic dysfunction appears mainly with relation to the artery occlude, if it is at level of branches of hepatic artery affecting only the subsegmental level the hepatic enzyme abnormalities are limited. Hepatic infarction occurring solely with cardiac failure are rare.

ISCHEMIC CHOLANGIOPATHY:

The bile duct as discussed earlier has the lone blood supply from the hepatic arteries only. Hence any abnormality in the hepatic blood flow can resulting from embolism,injury during surgery and hypotension resulting in circulatory failure can cause necrosis in the bile duct epithelium along with that of ischemic hepatitis. There occurs elevation alkaline phosphatase and gamma

glutamyl transferase enzyme elevation more than the transaminases if there is no associated ischemic hepatitis.

HEAT STROKE:

Heat stroke is very fatal condition affecting the whole body systems and fatality rates can reach upto 25-30%. The liver bears the brunt more in this condition since it is affected in two ways: hepatic necrosis due to elevated core body temperatre and also the associated hypotension. The liver enzymes are elevated with the elevation in AST being more than that of ALT . This happens because of the elevation in the other isoenzyme forms from brain,muscle, kidney. The recovery these enzymes takes much longer time than the ischemic hepatitis – over weeks . Bad prognostic indiactors are enormous elevationof enzymes as well as progressive rise in serum bilirubin.the histolgic picture includes that of zone 3 necrosis,steatosis,sinusoidal dilatation and cholangiolar proliferation.

PASSIVE CONGESTION:

Passive congestion occurs in individuals with isolated right heart failre, biventricular failure, cor pulmonale, chronic pulmonary embolism, valvular heart diseases,constrictive pericarditis. The histopathologic description of the liver in state of chronic congestion will be ; reddish central areas corresponding to central vein congestion and hemorrhage into zone 3

,surrounded by pale or yellowish areas of zone 1 or 2 with fatty changes, fibrosis around the central vein is seen and over course of time this fibrosis will become as a bridging fibrosis leading onto cirrhotic liver. Usually other types of cirrhosis have portal to portal fibrosis and also the hepatocytes around the portal regions may regenerate to form small nodules .The pathological alterations lead onto produce cardiac cirrhosis and high protein ascites. This ascites is formed due to the chronic congestion which causes the sinusoidal enlargement, space of Disse enlargement and collection of fluid thereby seeping into the peritoneal cavity forming ascites. This congestion also causes sinusoidal fibrosis preventing diffusion of oxygen and nutrients leading onto increased susceptibility of zone 3 necrosis of hepatocytes. Studies have proven that even though the patho- physiologic alterations can lead onto liver related mortality ,it is usually associated with left ventricular damage.

There are 3 ways of presentation in patients with passive congestion of liver :

1) Asymptomatic with mild elevation in serum bilirubin, INR and liver enzymes,
2) Dull right upper quadrant pain,
3) For evaluation of ascites

The common physical findings present are that of right ventricular failure like elevated Jugular Venous pressure, hepatojugular reflex,

hepatomegaly which will be tender, pulsations in the enlarged liver if tricuspid valvular abnormalities are present and also pedal edema.

The biochemical alterations in the passive congested state are mainly a mild elevation in the enzymes, serum bilirubin but these can be normal also. Serum biliribin elevation is frequently due to the unconjugated fraction and it is proven that the elevation parallels the severity of congestion and right atrial pressure elevation. Maximum value that can be attained is 20 mg/dl with severe congestion. Serum albumin level is typically normal or may be reduced to some extent. Prolongation of Prothrombin time is the most consistent alteration that take place in congested state and it resolves with that of reverting to normal circulatory state. Serum ammonia levels may be increased and all of these abnormalities tend to increase when there is associated left ventricular dysfunction.

Ascites is a frequent finding and it tends to be high protein fluid with the serum ascetic fluid albumin gradient more than 1.1 or ascetic fluid albumin more than 2.5 gm%. Another feature differentiating passive congestion induced ascites and liver disorder is the elevated free and wedged hepatic venous pressure with normal hepatic venous pressure gradient(HVPG). Patients with chronic passive congestion have relatively stable hepatic functions as compared to the patients with left heart disease which will affect the hepatic perfusion.

Treatment of this passive congestion is correction of underlying cardiac condition and also improving the forward cardiac ouput. Ascites is treated with diuretics taking care in preventing treatment and dehydration with large ascites being treated with paracentesis and surgical stenting procedures.

CONSTRICTIVE PERICARDITIS:

Constrictive pericarditis presents itself similar to that of the Budd Chiari syndrome where it will be associated with marked elevation of the central venous pressure which can cause zone 3 hepatic necrosis. The enzyme elevation and other biochemical abnormalities occur at much rapid rate than other forms of passive congestion. Eventhough there is elevation of enzymes , the increase in serum bilirubin is not seen as much. Pericardectomy can relieve the symptoms and can cause reversion of liver biochemistry.

LIVER BIOCHEMISTRY

ENZYMES THAT SERVE AS THE INDICATORS OF HEPATOCELLULAR NECROSIS

AMINOTRANSFERASES:

In cases of acute hepatocellular injury such as hepatitis, serum transaminases serve as the most useful markers of the liver cell injury Quantifying the formation of pyruvate and oxaloacetate which are the products of the aminotransferase reaction to their enzymatic reduction to lactate and malate is

one of the several techniques used for assessing the activities of ALT and AST in serum. Nicotinamide adenine dinulcleotide is formed as a result of the oxidation of the reduced form of nicotinamide adenine dinucleotide which in turn is the cofactor in this reduction reaction. This process can be easily found out by spectrophotometer as NADH losses its potential to absorb light at 340nm on conversion.

As per descending order of concentration AST is found in the liver, cardiac muscle, skeletal muscle, the kidneys, the brain, pancreas, the lungs, leukocytes and erythrocytes. On the other hand liver has the maximum levels of ALT. On the event of destruction of the tissues or due to permeability changes in the membrane the serum transaminases tend to increase. When aminotransferases are injected they get equally dispersed in interstitial fluid and in plasma from where they get broken down down by reticuloendothelial cells and are thus cleared off similar to other serum proteins. In this process AST is quickly metabolized than ALT and the hepatic sinusoidal cells are the main stay for AST clearance. Both biliary and urinary excretion do not account for ALT or AST clearance as there is no aminotransferases found in urine and only very minute quantities are being found in bile.

Pyridoxal 5'-phosphate serves as the cofactor for both ALT and AST and these transaminases exists in both apoenzyme and holoenzyme forms in serum. The site of existence of these transferases vary in tissues, as ALT exists only in

the cytosol while AST exists both in cytosol and in mitochondria. Both the forms of AST are true isoenzymes are deemed to be immunologically separate. By processes such as immunoprecipitation, chromatography and electrophoresis the two forms can be separated.The mitochondrial isoenzyme of AST contribute to 80% its activity in liver while the cytosolic isoenzyme remains as the major contributor to the circulating AST activity. The isoenzyme analysis of serum ALT and AST is hardly useful as they are not tissue specific except in patients with acute myocardial infarction or with chronic alcoholic liver disease. This is because, in myocardial infarction as an outcome of extreme tissue necrosis mitochondrial AST levels tend to increase and can be used as an indicator of the disease. The same happens in case of chronic alcoholic liver disease but not in acute alcoholic states.

Elevation of aminotransferases is noted in various conditions such as acute and chronic hepatitis, cirrhosis, infectious mononucleosis, heart failure, metastaic carcinoma, various infections and in some granulomatous liver disorders. Yet the peak elevations can be noticed in cases of extensive liver injury as in drug or viral hepatitis, in carbon tetrachloride or phaloidin (hepatotoxins) induced hepatotoxicity.In common , the levels increase in the low thousand. It is usually less than 300IU in alcoholic liver disease, and is rarely more than 500IU in conditions such as cirrhosis, obstructive jaundice, viral hepatitis in patients with immunodeficiency syndromes. When these levels go high as 10000

to15000IU/L the recovery is seldom good. Both ALT and AST are simultaneously increases in cases of hepatobiliary diseases with the ALT levels a little greater than the AST levels. In conducting epidemiological studies regarding viral hepatitis, ALT is used as a sensitive and specific indicator than AST levels.

Numerous queries have risen regarding the normal range of ALT values which was previously set in 1950's and has seldom changed then. Finally the normal range was the mean of values from a group of healthy individuals +/- 2SD. This would have led to a wrong interpretation of the data. Thus, the upper normal values were decreased to 3U/L for men and 19U/L for women, which in turn resulted in a drop in specificity from 97.4% to 88.5% and an increase in sensitivity from 55% to 76.3% in detecting hepatitis c viremia patients. The elevation of serum transaminases is a poor guide which has got very little correspondence to the extent of liver cell injury. The result of acute hepatocellular diseases is defectively portrayed by absolute elevation of aminotransferases. The random decrease in serum aminotransferase levels though indicates recovery from the disease on one hand; it also serves as a poor prognostic sign in massive destruction of liver cells as in fulminant hepatitis due to loss of viable hepatocytes.

Even in the early phases of hepatitis, elevation in serum transaminases is noted even before the rise of serum bilirubin levels. Hence a decreasing trend in aminotransferase levels is noted while there is an increasing

trend in bilirubin levels. This decrease is particularly noted in recovery stage of viral hepatitis. During the development of chronic hepatitis or in cases of recrudescence of acute hepatitis a secondary rise or a persistent elevation is noted. Both ALT and AST levels show variability in instance of infections such as Hepatitis C. The constant elevation in aminotransferases is most often noted with patients with chronic hepatitis as their liver biopsy feature. While on the other hand normal ALT and AST levels coupled with Hepatitis C infection also elicits chronic hepatitis a s the liver biopsy feature. Thus, the serial assessment of the levels of aminotransferases serve as useful tool in determining the clinical stage of hepatitis and also in measuring the response to immunosuppressive therapy given in cases of chronic hepatitis.

The significance of AST/ALT ratio is very little when used for differentiating the various causes of hepatobiliary diseases. Yet, it is still a sensitive indicator in alcoholic liver disease in which the ALT level is not more than 300IU and AST/ALT ratio is more than 2. When the ratio is more than 3 then it strongly suggests alcoholic liver disease. This is because ALT requires pyridoxal 5' phosphate for its synthesis much more than AST. This is reduced in alcoholics and hence the altered AST/ALT ratio in the liver is reflected in the serum ratio as well. The increase in ALT and AST levels is usually not more than 200IU and 300IU respectively in alcoholic liver disease. This is not properly substantiated by the reason that the hepatic concentrations are low. In alcoholic

liver disease associated with other states such as heart failure, drug toxicity the levels peak high to the range of thousands. In spite of which the AST/ALT ratio remains increased and is the outstanding feature of alcoholic liver disease.

The AST/ALT ratio has also been used in the study of chronic hepatitis C infection in which the ratio was used as a noninvasive marker of cirrhosis. The test revealed that cirrhosis developed when AST/ ALT ratio was greater than 1. The study had a higher specificity of (94%-100%) in spite of low sensitivity (44%-75%). This ratio existed because of the point that in cirrhosis patients the functional hepatic blood flow would get decreased, hence the uptake of AST by the hepatic sinusoids would have got decreased and thus this gets reflected as a rise in serum AST levels.

Increased levels of serum transaminases are not considered as pointers to hepatobiliary diseases. Even in other occasions, such as myocardial infarction where severe cardiac muscle damage occurs or in cases of skeletal muscle damage, the AST levels get elevated. On the other hand increase in ALT occurs in cardiac disease. This is seen in patients with large infarcts with congestive heart failure and circulatory collapse which would lead to hepatic ischemia and central hepatocellular necrosis resulting in release of ALT (hepatic origin).

In the instance of muscle disease increase in ALT and AST levels is noted. Yet the increase is usually less than 300U/L and rarely exceeds this

range except in cases of acute rhabdomyolysis. Rise in AST and ALT levels has also been recorded in persons doing vigorous exercise at the time of which the AST/ALT ratio initially is about 3:1 but then decrease to 1:1 owing to the short half life of AST. Similarly the ratio is around 1:1 in patients with chronic muscle disease.When old calorimetric tests are done drugs such as erythromycin or paraaminosalycylic acid can produce false elevation in aminotransferases. One such special situation is uremia, in which a low level of aminotransferases (AST) is seen. Once after dialysis the level of AST starts to rise up. This has brought out that a dialyzable inhibitor of aminotransferase reaction is present in uremic patients.

ISOCITRATE DEHYDROGENASE:

A cytoplasmic enzyme which is found in liver heart, kidneys, and skeletal muscle is Isocitrate dehydrogenase. This is a less sensitive indicator in acute and chronic hepatitis whose activity matches that of aminotransferases when through serum levels. As like glutamate dehydrogenase, isocitrate dehydrogenase is also a marker of centrilobular zone necrosis. This enzyme is also found to rise in conditions of disseminated malignant diseases in spite of normal liver functions. ICDH measurements in serum have shown no greater advantage than the measurements of aminotransferases in spite of its promotion asa marker of liver disease.

LACTATE DEHYDROGENASE:

Lactate dehydrogenase is an enzyme which is known to originate from tissues all over the body. It is a cytoplasmic enzyme and has got 5 isoenzymes in serum. By electrophoresis these isoenzymes are easily separated and the slowest moving isoenzyme is found in the liver. It is deemed as a useful indicator of myocardial infarction and hemolysis. In case of liver disease this enzyme has got poor specificity and sensitivity, even when its particular isoenzymes are assayed.

ENZYMES USED IN THE DETECTION OF CHOLESTASIS

ALKALINE PHOSPHATASE:

Though found in numerous sites all through the body such as bone osteoblasts, the canalicular membranes of hepatocytes, the brush border of the mucosal cells of the small intestine, the placenta, the white blood cells and the proximal convoluted tubules of the kidneys, the accurate function of this enzymes is not known. The alkaline phosphatase was known play an active role in rat liver by downregulating the secretion of intrahepatic biliary epithelium. Also it was found to be related to calcification of bones. Despite this its particular functions could not be demonstrated though at many sites it is said to involve in transport processes. The serum levels of alkaline phosphatase reflect its activity. The source of alkaline phosphatase is mainly

derived from three sites- the liver, bone and the intestinal tract (rarely) of which the liver and the bone stand out to be important sources. When infused, the alkaline phosphatase had a half-life of 7 days and was found that it also behaves similar to other serum proteins. The site of destruction of these enzymes is not known but its clearance was found to be independent of the patency of the bile ducts and of the functional status of the liver.

Various procedures are used to measure the alkaline phosphatase activity. Using ρ-nitrophenylphosphate as substrate and an amino alcohol (2-amino-2-methyl-1-propanol) as a buffer a procedure is done in which the rate of release of ρ-nitrophenol or phosphate is measured in the presence of specified incubation conditions. The activity of alkaline phosphatase that produces 1mmol of chromogen or inorganic phosphate per minute is defined as international units in which alkaline phosphatases levels are expressed. Numerous clinical diseases could be detected by way of the results obtained by the above procedures. Alkaline phosphatase has a variety of isoenzymes hence the reaction of these enzymes are different in different assay systems. So even if a conversion factor is used to interchange the values obtained by different procedures the resultant correlation between these values is very poor in any individual. Thus by expressing the results obtained as multiples of the upper limit of normal the results could be compared. The concentration of phosphate,

citrate, and magnesium and the type and concentration of the buffer has got significance as numerous analytic sources of error can occur.

When the mean alkaline phosphatase levels are measured, it is found to be a little higher in men when compared to the women individuals in the age group of 15- 50 years. While the levels are found somewhat equal in both men and women in people more than 60 years of age and are also a little higher than compared to that of younger individuals. This variation can never be explained. In young children due to growth of bones there is an influx of enzymes from osteoid tissues resulting in elevated levels of alkaline phosphatase and is equal in both the sexes. Even in the absence of hepatobiliary diseases the levels of alkaline phosphatase can reach upto three times that of an adult in case of a healthy adolescent individual. In normal pregnancy the levels are found to double due to the inputs from that of placental phosphates.

Physiologically the levels of alkaline phosphatase is high during growth and in pregnancy. Pathologically elevations can occur in bone diseases due to active osteoblasts as that of elevations seen in hepatobiliary diseases. Elevations in alkaline phosphatase are seldom caused by the intestinal tract and the kidneys.

Gamma glutamyl transpeptidase : (GGT)

GGT is present in the liver, spleen, heart, brain, kidneys and vesicles being present in normal serum. Elevated GGT levels are seen in diseases of liver,biliary tract and pancreas which are usually correlate with the alkaline phosphatase levels.GGT levels are useful because they are not related to any bone diasease and are high in alcoholic liver diseases when other enzymes are normal.GGT levels easily correlate with severity of alcoholic hepatitis than others.GGT levels confer specificity to liver when ALP is elevated .

Serum albumin :

Average adult albumin levels vary from 300 to 500 gram synthesized by liver.The rate of synthesis depends upon the loss or decrease due to dilution in disease states and regulated by nutritional status, osmotic pressure, systemic inflammation and hormone levels. It's synthesis is stimulated by aminoacids like tryptophan, arginine,ornithine, corticosteroids,thyroxine and urea synthesis while alchol decreases its synthesis.Levels less than 3gram % should arise suspicion of chronic hepatitis and also ischemic hepatitis.

Prothrombin Time :

Clotting is a complex mechanism which involves various factors like Factor II,VII,IX,X requiring Vitamin K for the synthesis by the liver. The Vitamin K dependent gamma carboxylation of the factors are

deranged in hepatic disorders releasing abnormal Prothrombin in the circulation.This abnormal Prothrombin levels can be useful even in absence of prolongation of the PT-INR ratios. Hypovitaminosis K can be present in the obstructive hepatic states,deficiency in diets,antibiotics intake and parenchymal liver diseases. PT-INR elevation has significant prognostic values in terms of acute hepatic decompensation and the improvement of atleast 30% in values shows that the parenchymal function is good.

METHODS AND MATERIALS

This study on the prevalence and assessment of individual tests of the liver function tests in the heart failure patients was done in the department of medicine, Tirunelveli medical college from may of 2016 to the the june of 2017 with the help of various departments like cardiology ,radiology and laboratory support. The precise reason of the study was to prove the alterations in liver functions which happens with various forms of heart failure and to use the results to assess,correlate with the severity of heart failure leading onto the easy prediction of severity of heart failure using liver function tests along with the clinical features even in absence of echocardiographic assessment.

This study was done with the consent of 50 people who were suffering from heart failure selected with the help of Framingham criteria for diagnosis of heart failure and also divide with help of echocardiographic assessment into two sets of patients ,namely, one with reduced ejection fraction (<40%) and next with preserved ejection fraction (>40%). All the required approval were sought and bought from the concerned departments along with the ethical approval from the respective college ethical committee and proceeded. The patients were taken up for study after doing the required laboratory and radiological assessment including ultrasound abdomen , echocardiogram (ejection fraction and diastolic dysfunction grading) after strict adherence to the inclusion and exclusion criteria. An oral consent was obtained

from patients and also attenders in case the patient was obtunded during the study, after explaining to them the nature of the study which does not interfere with management of the patient.

INCLUSION CRITERIA:

Acute heart failure

Chronic heart failure

EXCLUSION CRITERIA:

Primary liver disease including infective liver diseases

Cirrhotic patients

Malignancy

Alcoholics

A patients were first asked about the personal details and then were asked about the specific symptoms of dyspnoea,orthopnoea, PND,chest pain.fatiguability,exercise intolerance ,ankle edema,jaundice,abdominal distension ,dilated neck veins and night coughs.they were enquired about their previous hospitalizations, drug intake,liver diaseases, blood transfusions, STD diseases history ,alcoholism and treatment history if any.

Then the patient was examined for elevation in jugular venous pressure, low blood pressure,tachycardia along with the routine general examination .the cardiovascular system examination was done carefully to look for signs of left as well right ventricular failure and if so they were included in

this study. Other system examination included looking for congestive liver enlargement, pleural effusion along with the routine .

Laboratory evaluations were done with normal routine investigations of complete hemogram, urine routine tests, renal function and special emphasis was laid on liver function tests with the all the components of LFT done along with the screening for hepatitis and HIV. Serum enzymes like AST, ALT, ALP, GGT levels were taken as elevated when exceeding the 4 times the normal levels as explained in the review of literature above. Ultrasound abdomen was done for congestion of the liver while echocardiogram was done to diagnose the heart failure with reduced and preserved ejection fraction for classification along with assessment of diastolic dysfunction in terms of normally practiced grading of 1 to 4 using the tissue and pulse Doppler techniques in echocardiogram.

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer programming using Epidemiological Information Package (EPI 2010) developed by Centre for Disease Control, Atlanta, USA.

OBSERVATION AND RESULTS

GROUP STATISTICS

	GROUP	N	Mean	Std. Deviation	P value
AGE	Group 1	32	58.91	11.13	0.004
	Group 2	18	67.67	7.40	
TOTAL BILIRUBIN	Group 1	32	2.07	1.35	0.186
	Group 2	18	1.58	1.02	
INDIRECT BILIRUBIN	Group 1	32	1.58	1.01	0.05
	Group 2	18	1.07	0.51	
DIRECT BILIRUBIN	Group 1	32	0.48	0.40	0.823
	Group 2	18	0.51	0.53	
ALT	Group 1	32	404.47	395.12	0.003
	Group 2	18	104.22	147.78	
AST	Group 1	32	361.56	350.38	0.004
	Group 2	18	102.78	129.30	
GGT	Group 1	32	122.31	152.11	0.242
	Group 2	18	181.56	197.74	
ALP	Group 1	32	127.31	170.20	0.378
	Group 2	18	174.06	192.56	
ALBUMIN	Group 1	32	3.35	0.77	0.281
	Group 2	18	3.57	0.40	
PT_INR	Group 1	32	1.05	0.24	0.971
	Group 2	18	1.06	0.20	
EF	Group 1	32	26.34	6.72	

PART 1

HEART FAILURE WITH REDUCED EJECTION FRACTION

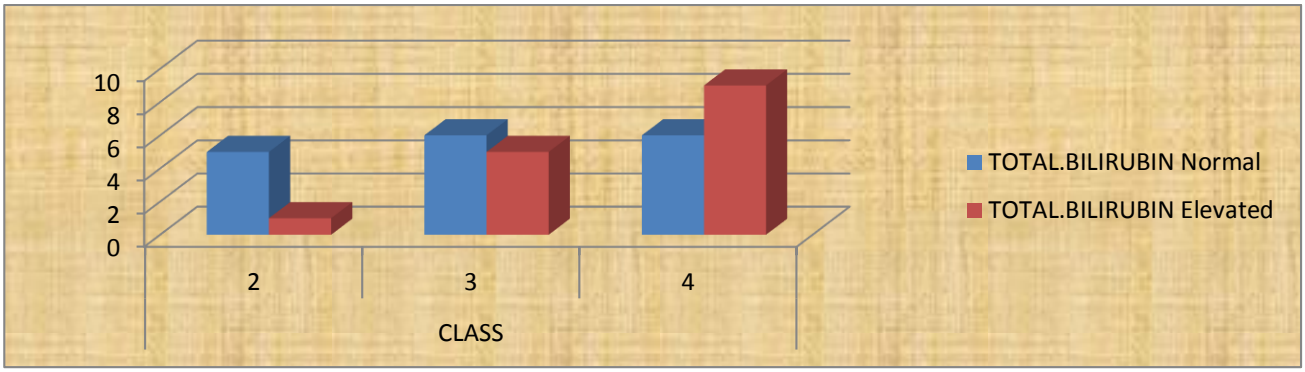
	Class	N	Mean	Std. Deviation	P value
TOTAL BILIRUBIN	2	6	1.47	1.34	0.212
	3	11	1.81	1.16	
	4	15	2.50	1.42	
INDIRECT BILIRUBIN	2	6	1.17	1.10	0.312
	3	11	1.43	0.92	
	4	15	1.86	1.03	
DIRECT BILIRUBIN	2	6	0.30	0.25	0.147
	3	11	0.38	0.36	
	4	15	0.63	0.45	
ALT	2	6	50.00	6.07	<0.0001
	3	11	200.82	341.84	
	4	15	695.60	291.48	
AST	2	6	45.00	3.79	<0.0001
	3	11	174.45	291.48	
	4	15	625.40	257.11	
GGT	2	6	120.67	163.65	0.193
	3	11	59.18	6.78	
	4	15	169.27	190.10	
ALP	2	6	114.33	146.88	0.132
	3	11	52.36	8.24	
	4	15	187.47	219.15	
ALBUMIN	2	6	3.52	0.77	0.006
	3	11	3.85	0.61	
	4	15	2.93	0.67	
PTINR	2	6	0.98	0.12	0.003
	3	11	0.90	0.06	
	4	15	1.19	0.28	

	Mean	Standard. Deviation
EF	26.34	6.72
TOTBILIRUBIN	2.07	1.35
INDIRECT BILIRUBIN	1.58	1.01
DIRECT.BILIRUBIN	0.48	0.40
ALT	404.47	395.12
AST	361.56	350.38
GGT	122.31	152.11
ALP	127.31	170.20
ALBUMIN	3.35	0.77
PROTHROMBIN TIME-INR	1.05	0.24

CORRELATION:

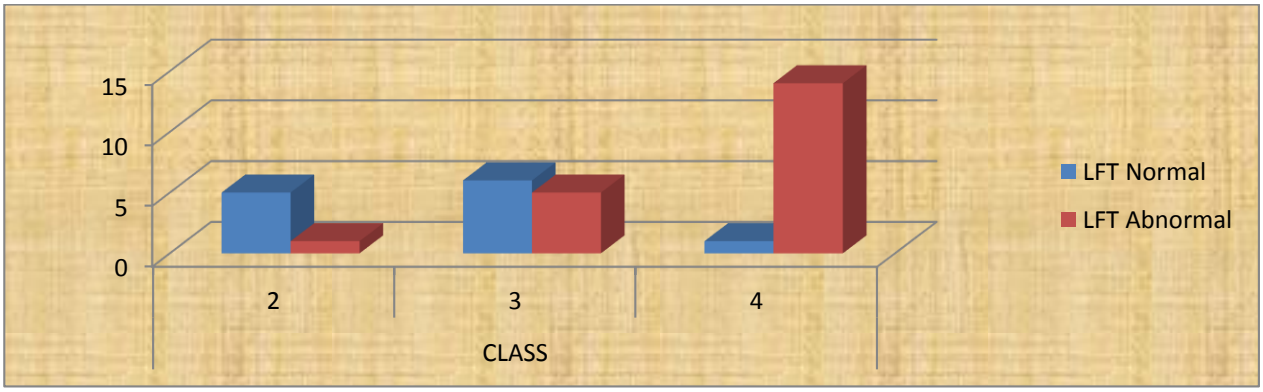
A) NYHA CLASS VS TOTAL BILIRUBIN:

NYHA CLASS	TOTAL.BILIRUBIN		
	Normal	Elevated	P value
2	5	1	0.197
3	6	5	
4	6	9	
TOTAL	17	15	



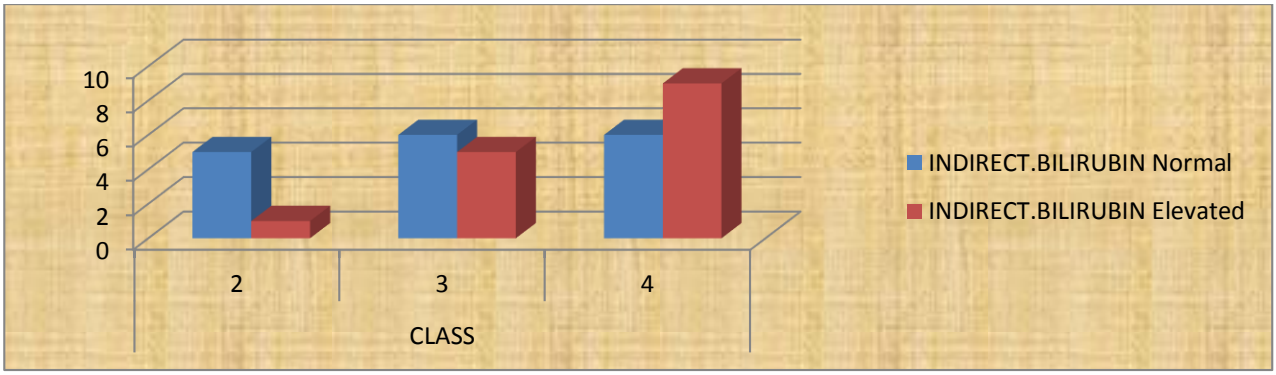
B) NYHA CLASS VS LIVER FUNCTION TEST:

LFT	NYHA CLASS			P value
	2	3	4	
Normal	5	6	1	0.002
Abnormal	1	5	14	



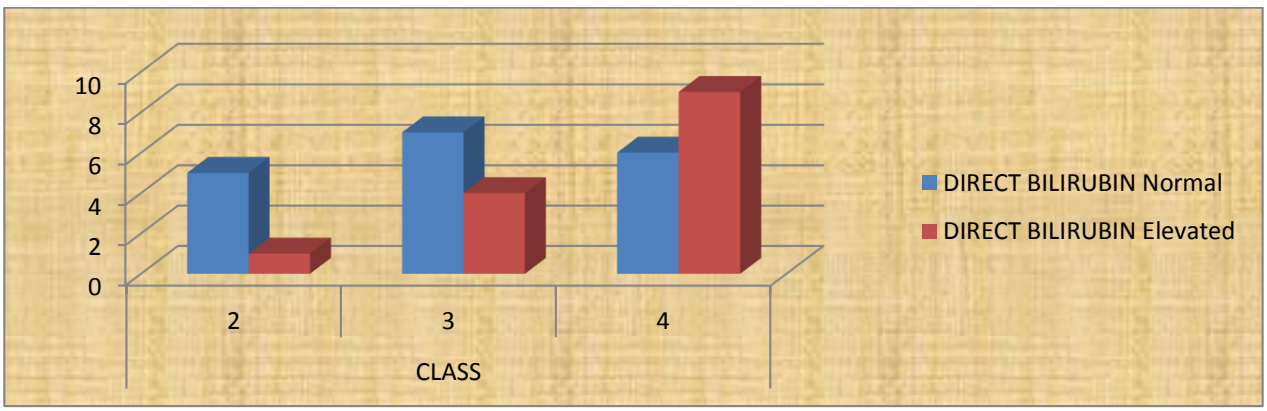
C) NYHA CLASS VS INDIRECT BILIRUBIN

NYHA CLASS	INDIRECT.BILIRUBIN		
	Normal	Elevated	P value
2	5	1	
3	6	5	
4	6	9	0.197



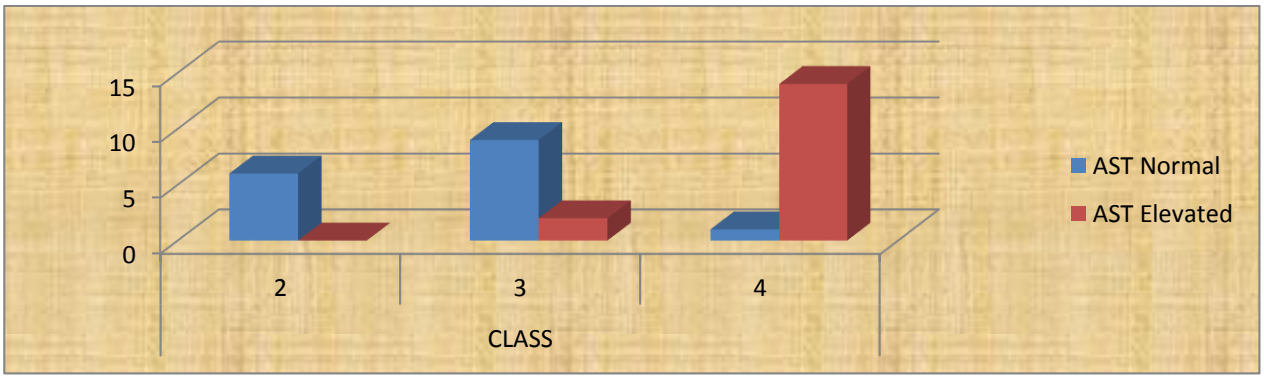
D) NYHA CLASS VS DIRECT BILIRUBIN:

NYHA CLASS	DIRECT BILIRUBIN		
	Normal	Elevated	P value
B	5	1	
C	7	4	
D	6	9	0.162
TOTAL	18	14	



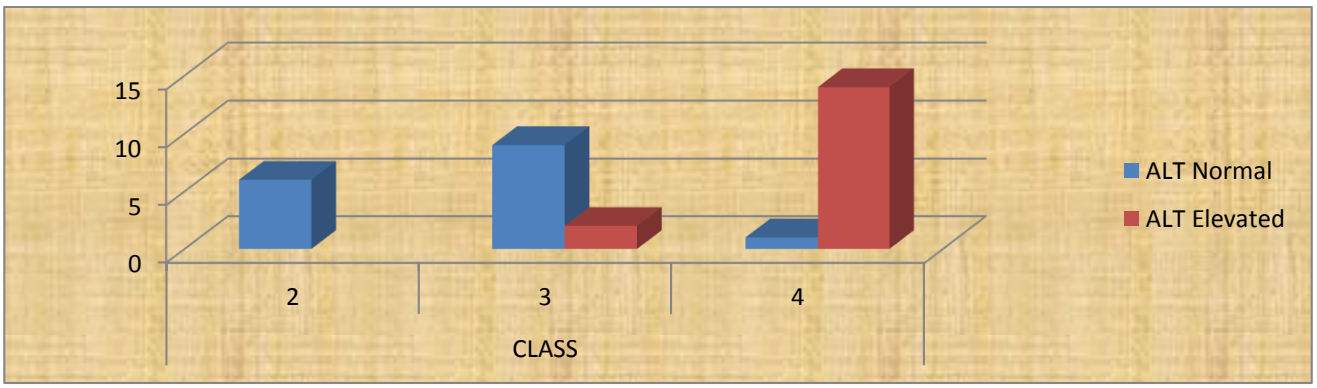
E)NYHA CLASS VS ASPARTATE TRANSAMINASE:

NYHA CLASS	AST		P value
	Normal	Elevated	
2	6	0	<0.0001
3	9	2	
4	1	14	
TOTAL	16	16	



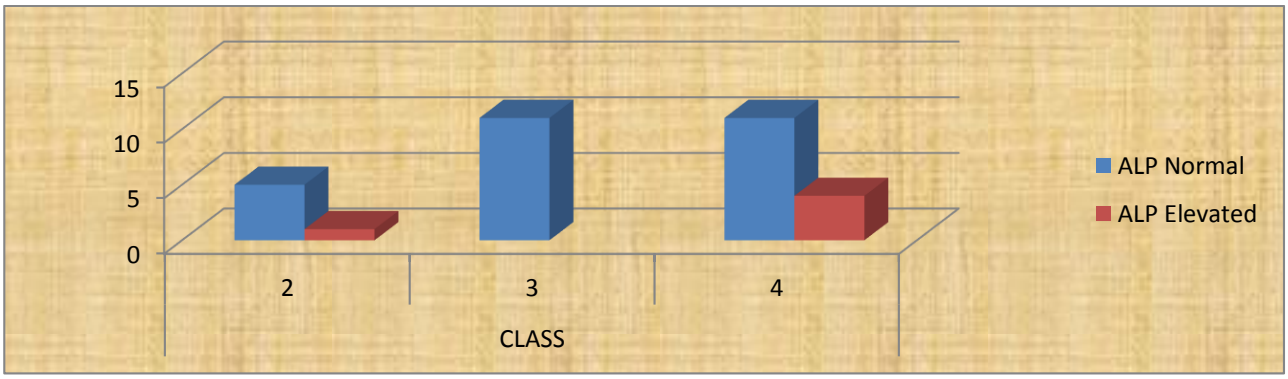
F)NYHA CLASS VERSUS ALANINE TRANSAMINASE:

NYHA CLASS	ALT		P value
	Normal	Elevated	
2	6	0	<0.0001
3	9	2	
4	1	14	
TOTAL	16	16	



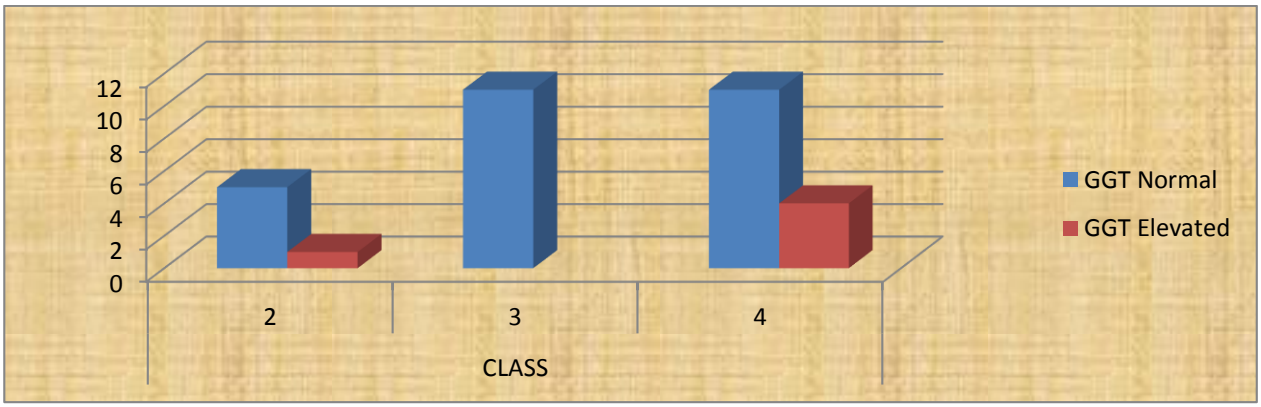
G)NYHA CLASS VS ALKALINE PHOSPHATASE :

NYHA CLASS	ALP		P value
	Normal	Elevated	
2	5	1	0.18
3	11	0	
4	11	4	
TOTAL	27	5	



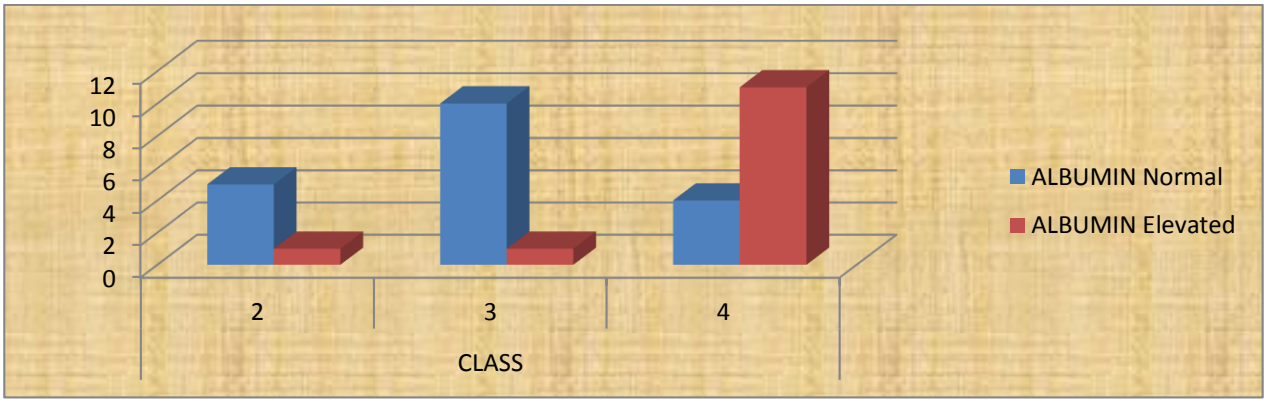
H)NYHA CLASS VS GAMMA GLUTAMYL TRANSFERASE:

NYHA CLASS	GGT		P value
	Normal	Elevated	
2	5	1	0.18
3	11	0	
4	11	4	
TOTAL	27	5	



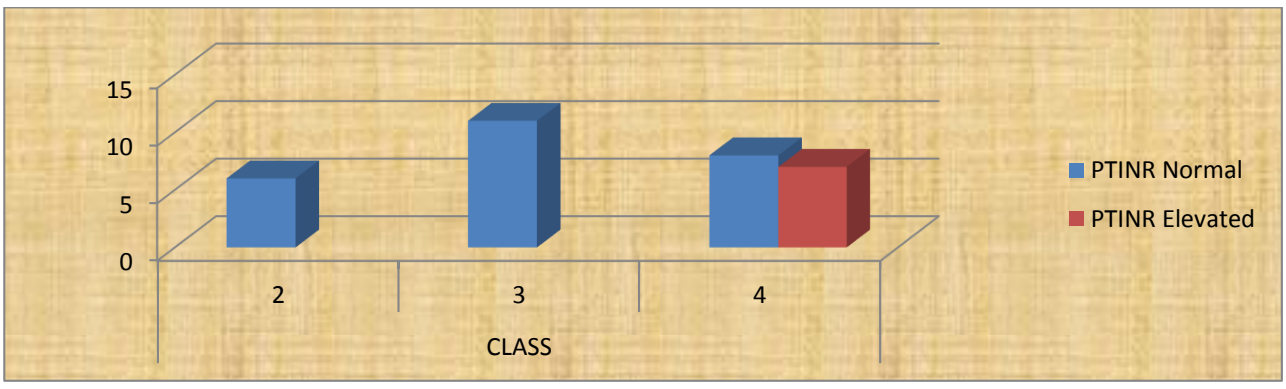
I) NYHA CLASS VS SERUM ALBUMIN :

NYHA CLASS	ALBUMIN		P value
	Normal	Elevated	
2	5	1	0.002
3	10	1	
4	4	11	
TOTAL	19	13	



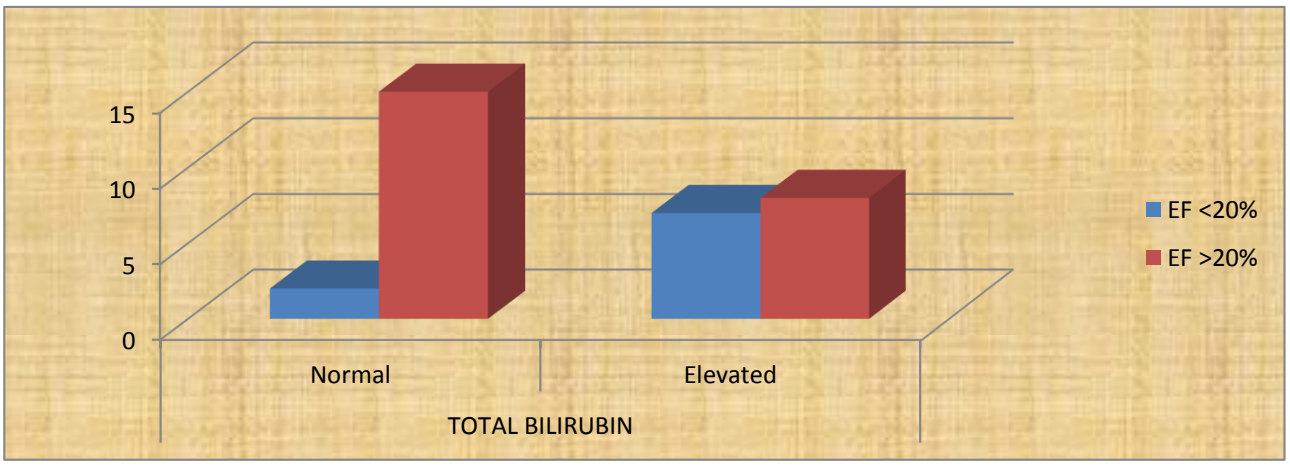
J)NYHA CLASS VS PROTHROMBIN TIME:

NYHA CLASS	PTINR		P value
	Normal	Elevated	
2	6	0	0.006
3	11	0	
4	8	7	
TOTAL	25	7	



K) EJECTION FRACTION VS TOTAL BILIRUBIN:

EJECTION FRACTION	TOTAL BILIRUBIN		P value
	Normal	Elevated	
<20%	2	7	0.028
>20%	15	8	
TOTAL	17	15	

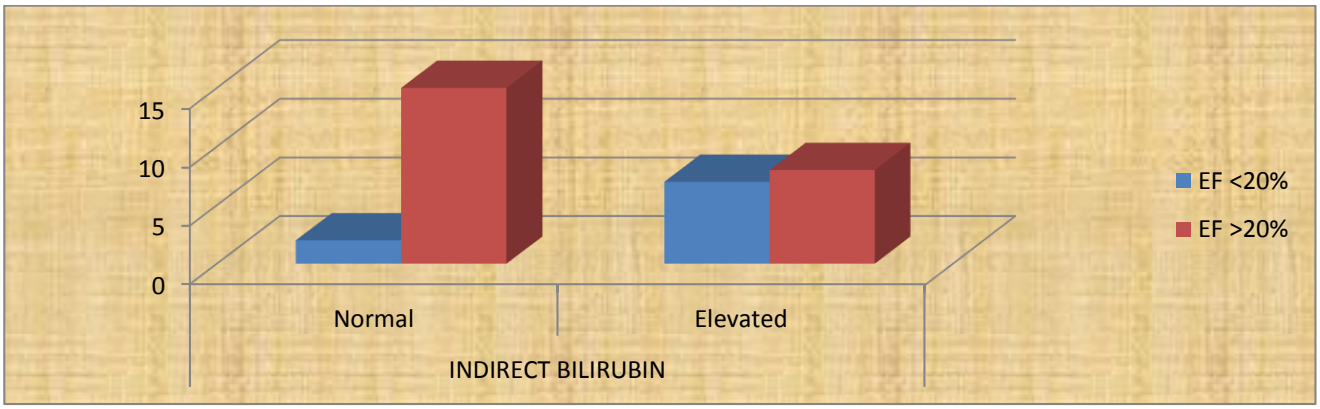


L) EJECTION FRACTION CORRELATION WITH ABNORMAL LFT:

	EF vs LFT	
Correlations	Pearson Correlation	-0.569
	P value	<0.0001

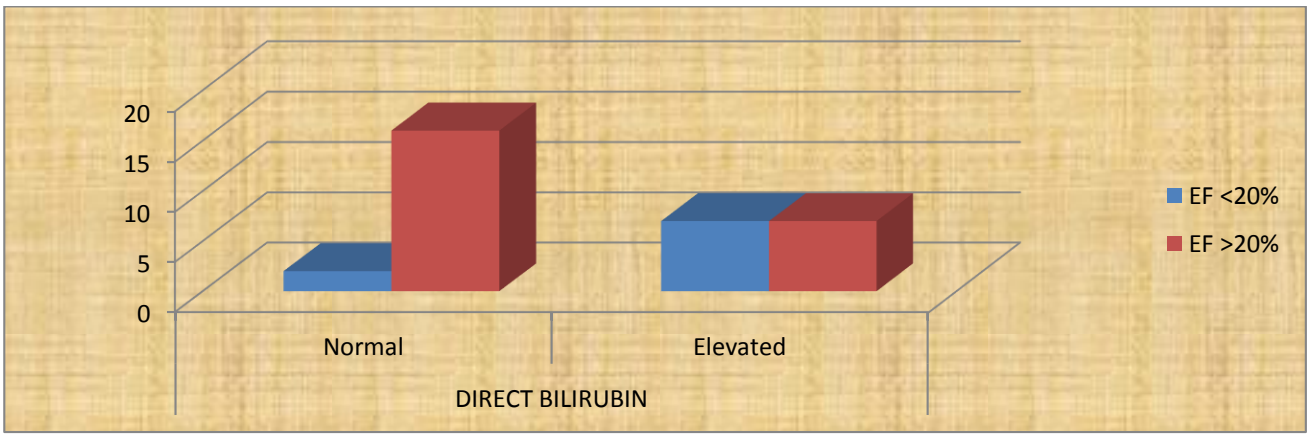
M) EJECTION FRACTION VS INDIRECT BILIRUBIN:

EJECTION FRACTION	INDIRECT BILIRUBIN		P value
	Normal	Elevated	
<20%	2	7	0.028
>20%	15	8	
TOTAL	17	15	



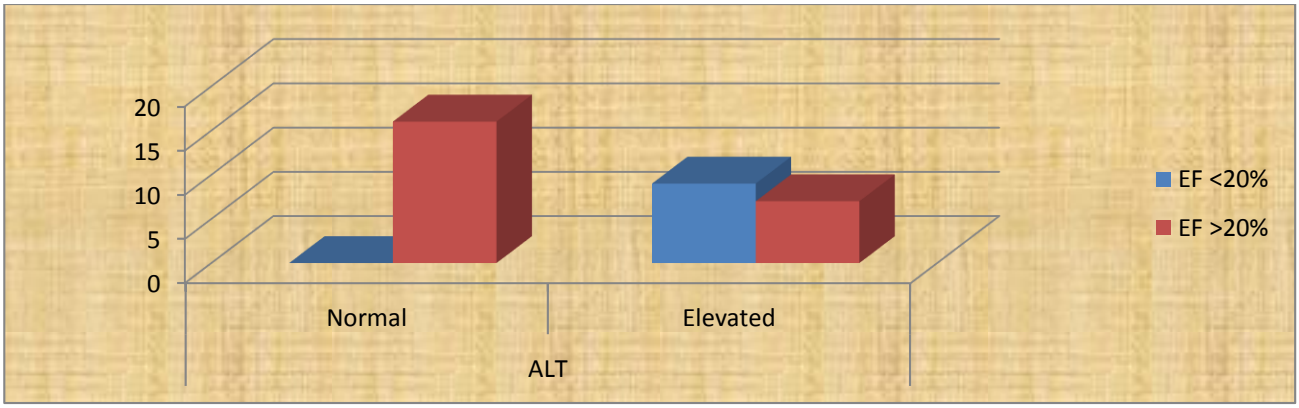
N) EJECTION FRACTION VERSUS DIRECT BILIRUBIN:

EJECTION FRACTION	DIRECT BILIRUBIN		P value
	Normal	Elevated	
<20%	2	7	0.015
>20%	16	7	
TOTAL	18	14	



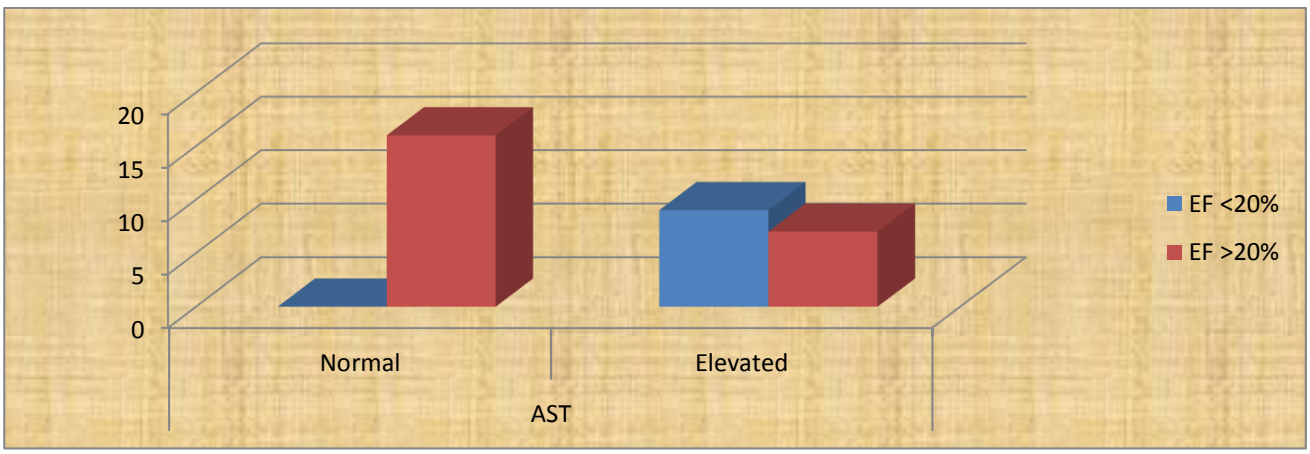
O) EJECTION FRACTION VS ALANINE TRANSAMINASE:

EJECTION FRACTION	ALT		P value
	Normal	Elevated	
<20%	0	9	<0.0001
>20%	16	7	
TOTAL	16	16	



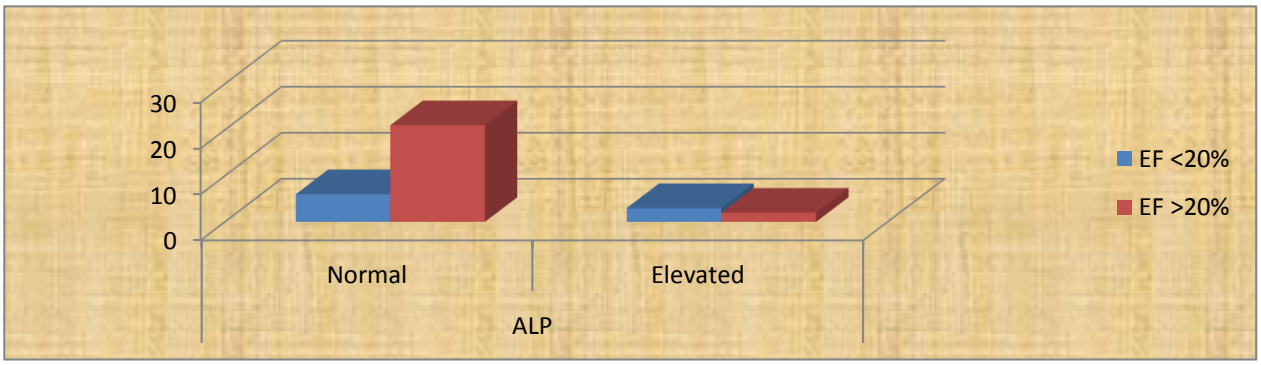
P) EJECTION FRACTION VS ASPARTATE TRANSAMINASE:

EJECTION FRACTION	AST		P value
	Normal	Elevated	
<20%	0	9	<0.0001
>20%	16	7	
TOTAL	16	16	



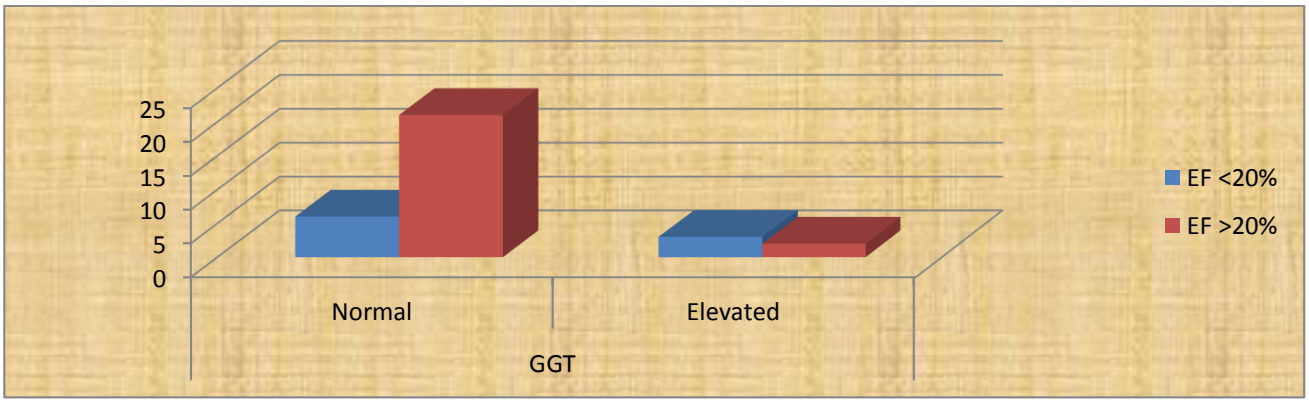
Q) EJECTION FRACTION VERSUS ALKALINE PHOSPHATASE:

EJECTION FRACTION	ALP		P value
	Normal	Elevated	
<20%	6	3	0.084
>20%	21	2	
TOTAL	27	5	



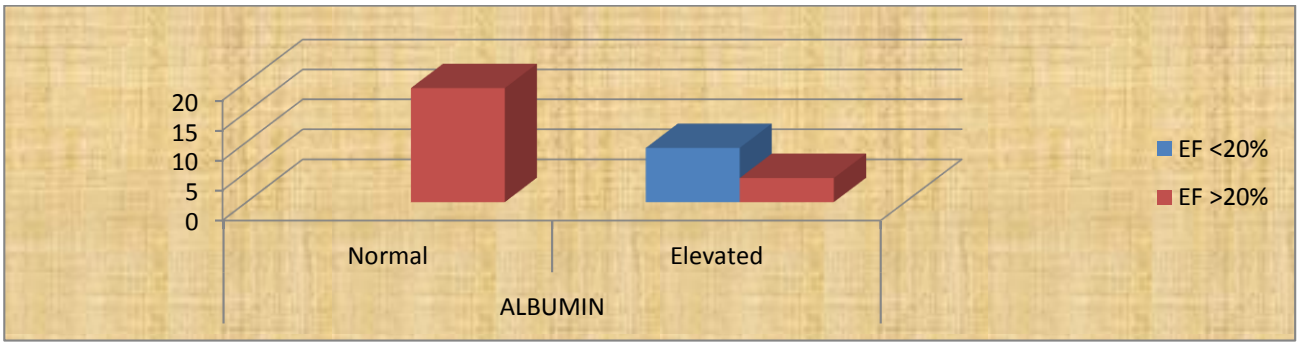
R) EJECTION FRACTION VERSUS GAMMA GLUTAMYL TRANSFERASE:

EJECTION FRACTION	GGT		
	Normal	Elevated	P value
<20%	6	3	0.084
>20%	21	2	
TOTAL	27	5	



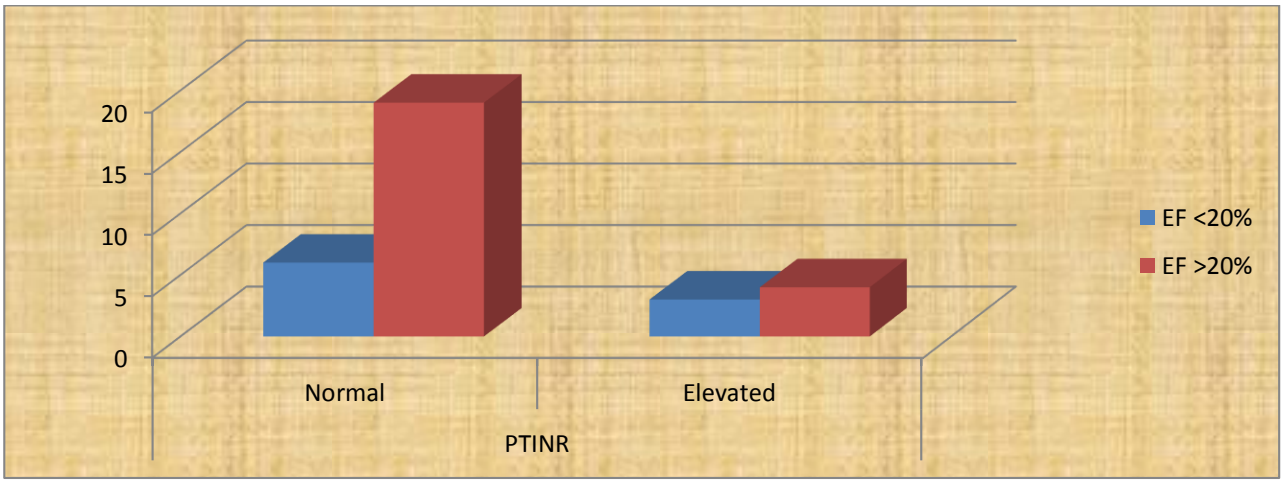
S)EJECTION FRACTION VS SERUM ALBUMIN:

EJECTION FRACTION	ALBUMIN		P value
	Normal	Elevated	
<20%	0	9	<0.0001
>20%	19	4	
TOTAL	19	13	



T)EJECTION FRACTION VS PROTHROMBIN TIME:

EJECTION FRACTION	PT-INR		P value
	Normal	Elevated	
<20%	6	3	0.327
>20%	19	4	
TOTAL	25	7	



CORRELATION SIGNIFICANCEOF EACH UNITS		EJECTION FRACTION
TOTAL BILIRUBIN	Pearson Correlation	-0.40
	P value	0.024
INDIRECT BILIRUBIN	Pearson Correlation	-0.37
	P value	0.036
DIRECT BILIRUBIN	Pearson Correlation	-0.37
	P value	0.036
ALT	Pearson Correlation	-0.77
	P value	0.000
AST	Pearson Correlation	-0.77
	P value	0.000
GGT	Pearson Correlation	-0.27
	P value	0.139
ALP	Pearson Correlation	-0.28
	P value	0.115
SERUM ALBUMIN	Pearson Correlation	0.59
	P value	0.000
PT-INR	Pearson Correlation	-0.30
	P value	0.097

The Pearson correlation of negative values implies the negative correlation of two variables , for example , a value of -0.77 of ALT enzyme explains that with decreasing ejection fraction there will be elevation of ALT enzymes in HFrEF than ALP which has lesser correlation value of -0.28.

PART -2

HEART FAILURE WITH PRESERVED EJECTION FRACTION

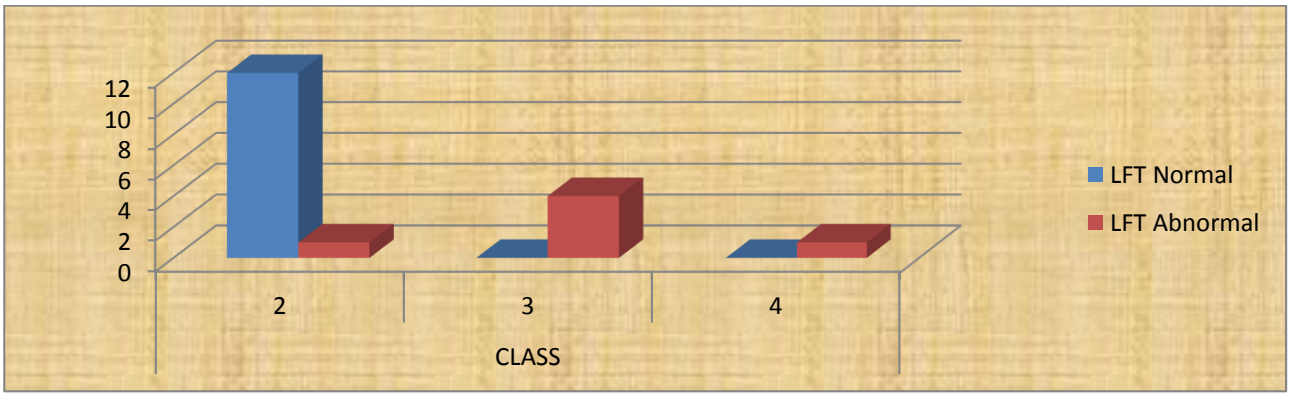
GROUP STATISTICS :

LFT	NYHA CLASS	N	Mean	Std. Deviation	P value
TOTAL.BILIRUBIN	2	13	1.14	0.57	0.004
	3	4	2.60	1.24	
INDIRECT BILIRUBIN	2	13	0.86	0.30	0.012
	3	4	1.50	0.64	
DIRECT BILIRUBIN	2	13	0.28	0.28	0.002
	3	4	1.10	0.64	
ALT	2	13	52.00	17.74	0.048
	3	4	196.50	259.50	
AST	2	13	56.54	12.71	0.044
	3	4	182.50	223.17	
GGT	2	13	63.38	13.44	<0.0001
	3	4	487.50	54.78	
ALP	2	13	59.62	15.24	<0.0001
	3	4	470.00	69.82	
SERUM ALBUMIN	2	13	3.69	0.26	0.001
	3	4	3.05	0.39	
PTINR	2	13	0.99	0.10	0.026
	3	4	1.25	0.35	

NYHA CLASS STATISTICS:

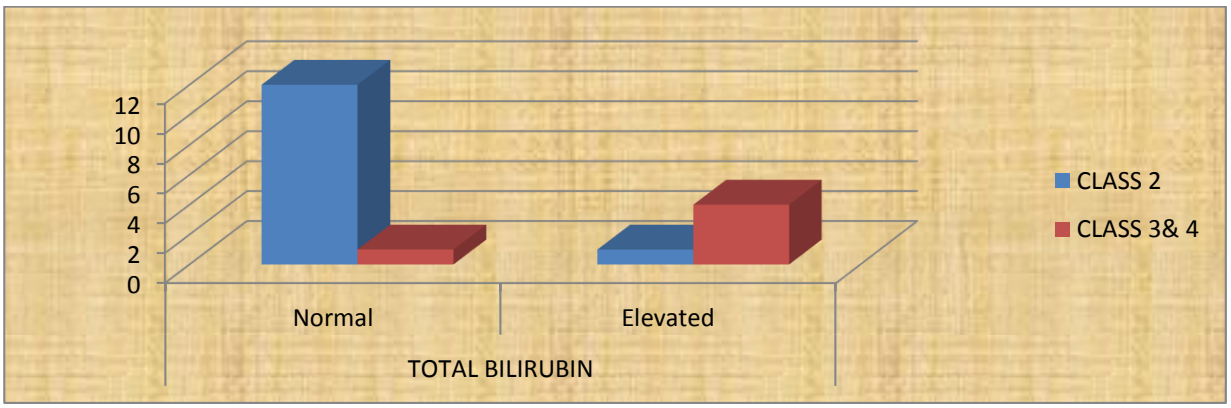
1) NYHA CLASS VS LFT:

LFT	CLASS			P value
	2	3	4	
Normal	12	0	0	0.001
Abnormal	1	4	1	



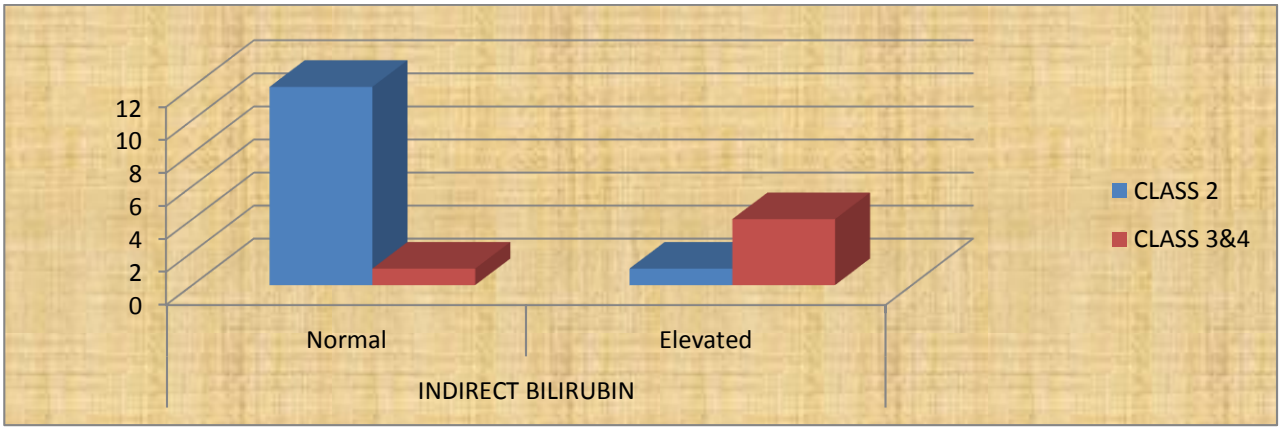
2) NYHA CLASS VS TOTAL BILIRUBIN:

CLASS	TOTAL BILIRUBIN		P value
	Normal	Elevated	
2	12	1	0.008
3&4	1	4	
TOTAL	13	5	



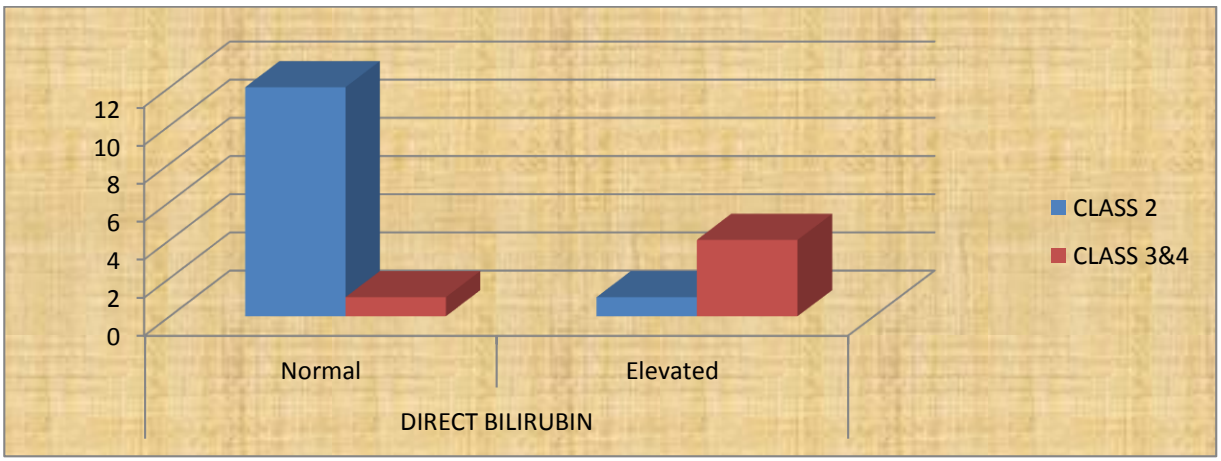
3) NYHA CLASS VS INDIRECT BILIRUBIN:

CLASS	INDIRECT BILIRUBIN		P value
	Normal	Elevated	
2	12	1	0.008
3&4	1	4	
TOTAL	13	5	



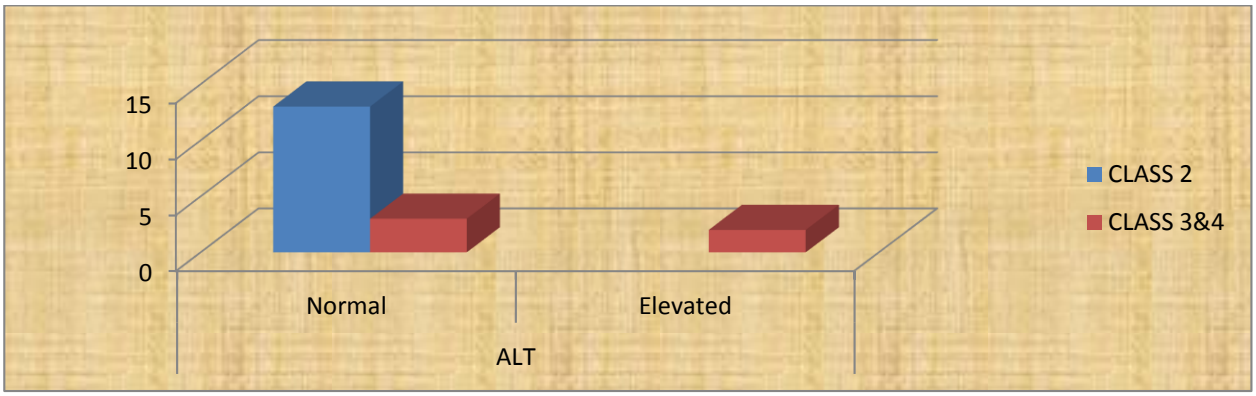
4) NYHA CLASS VS DIRECT BILIRUBIN:

CLASS	DIRECT BILIRUBIN		P value
	Normal	Elevated	
2	12	1	0.008
3& 4	1	4	
TOTAL	13	5	



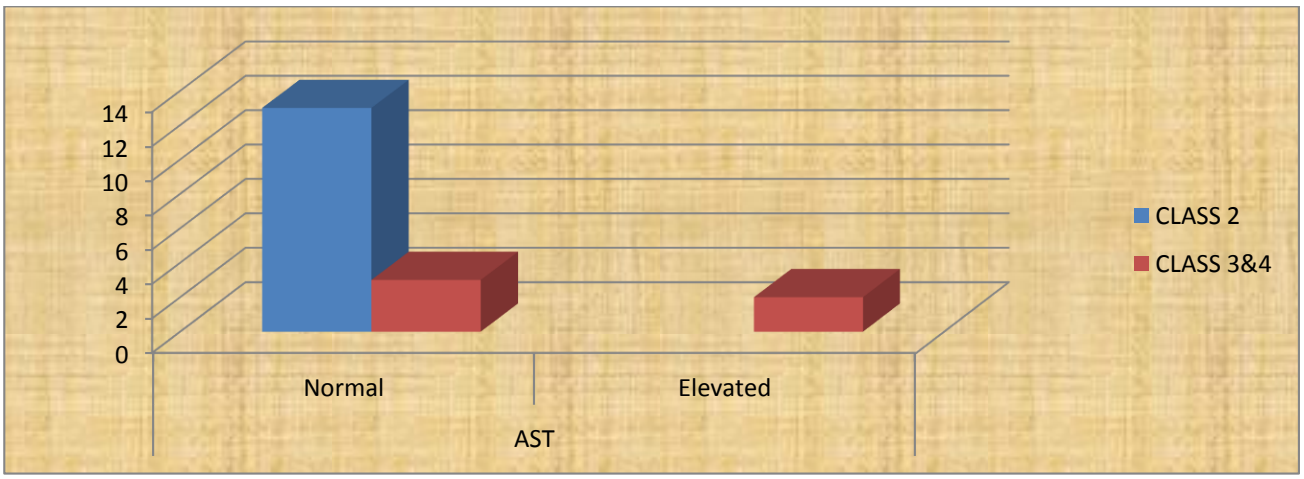
5) NYHA CLASS VS ALT:

CLASS	ALT		P value
	Normal	Elevated	
2	13	0	0.065
3&4	3	2	
TOTAL	16	2	



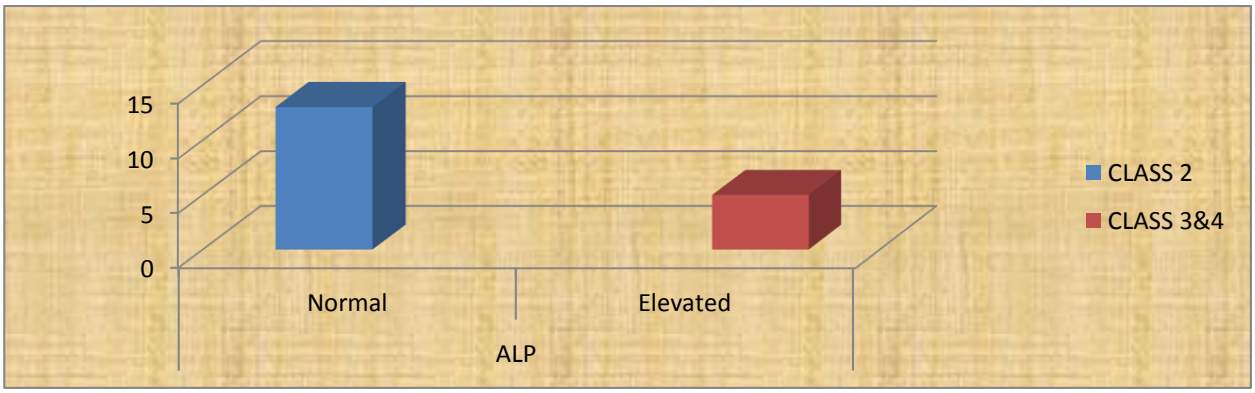
6) NYHA CLASS VS AST:

CLASS	AST		P value
	Normal	Elevated	
2	13	0	0.065
3&4	3	2	
TOTAL	16	2	



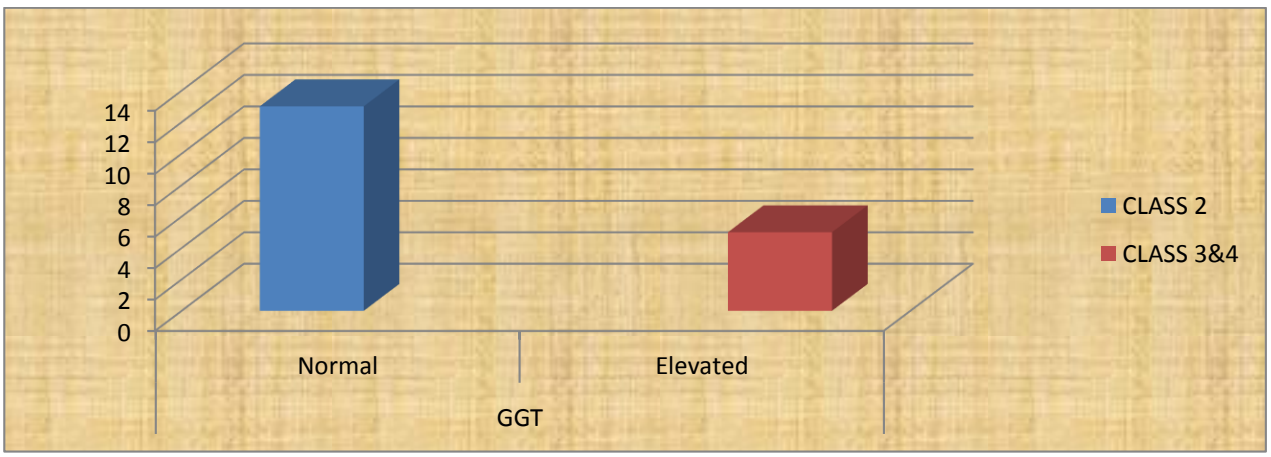
7) NYHA CLASS VS ALT:

CLASS	ALP		P value
	Normal	Elevated	
2	13	0	<0.0001
3&4	0	5	
TOTAL	13	5	



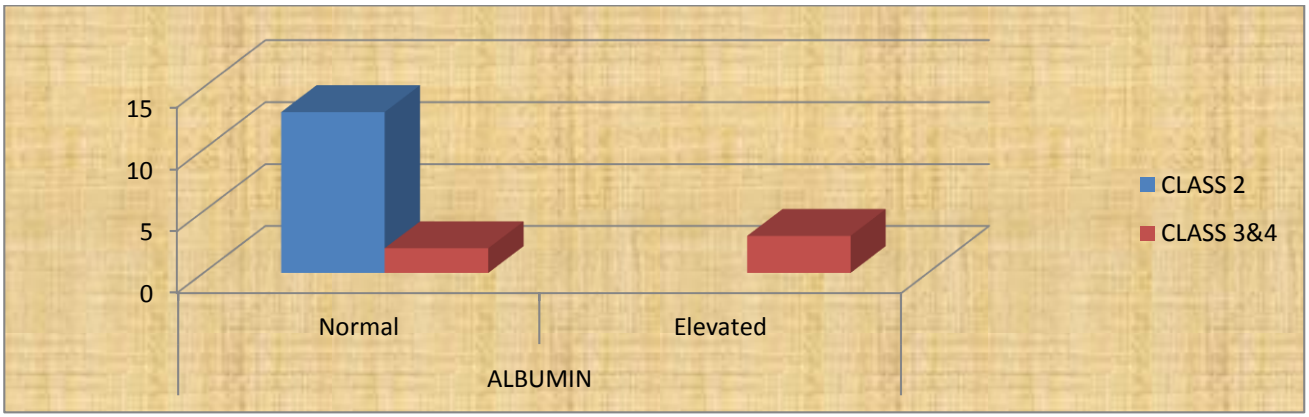
8)NYHA CLASS VS GGT:

CLASS	GGT		P value
	Normal	Elevated	
2	13	0	<0.0001
3&4	0	5	
TOTAL	13	5	



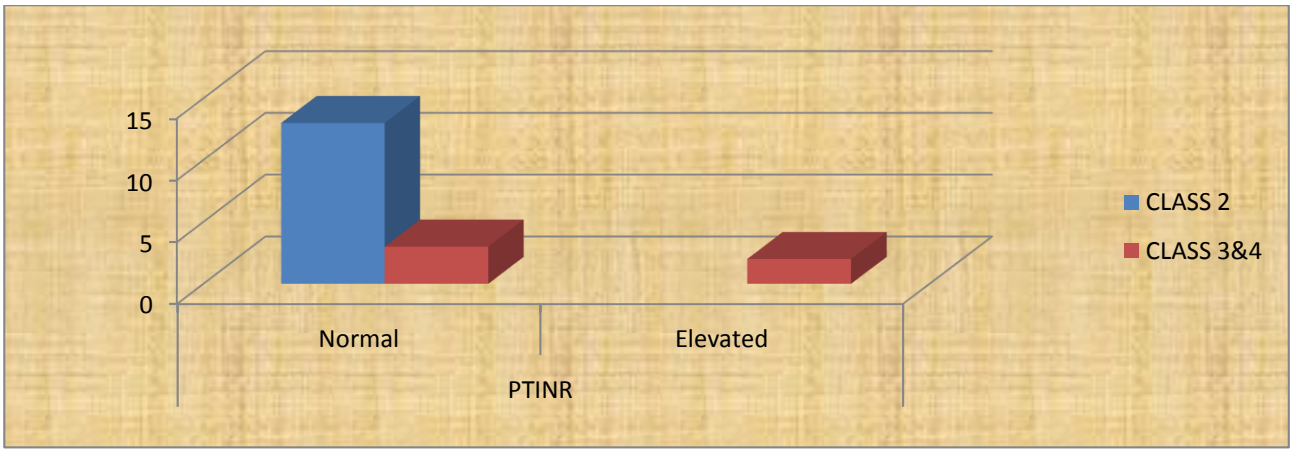
9) NYHA CLASS VS SERUM ALBUMIN :

CLASS	ALBUMIN		P value
	Normal	Elevated	
2	13	0	0.012
3&4	2	3	
TOTAL	15	3	



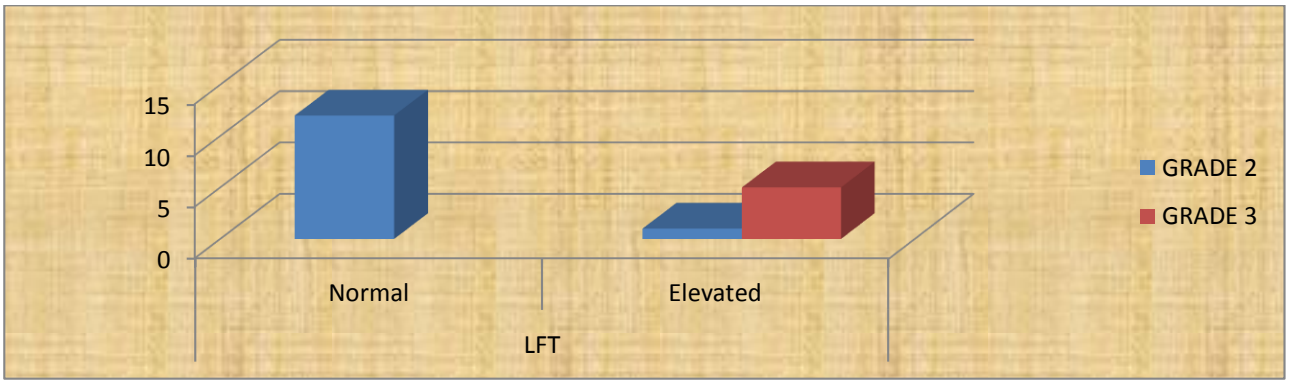
10) NYHA CLASS VS PROTHROMBIN TIME:

CLASS	PTINR		P value
	Normal	Elevated	
2	13	0	0.065
3&4	3	2	
TOTAL	16	2	



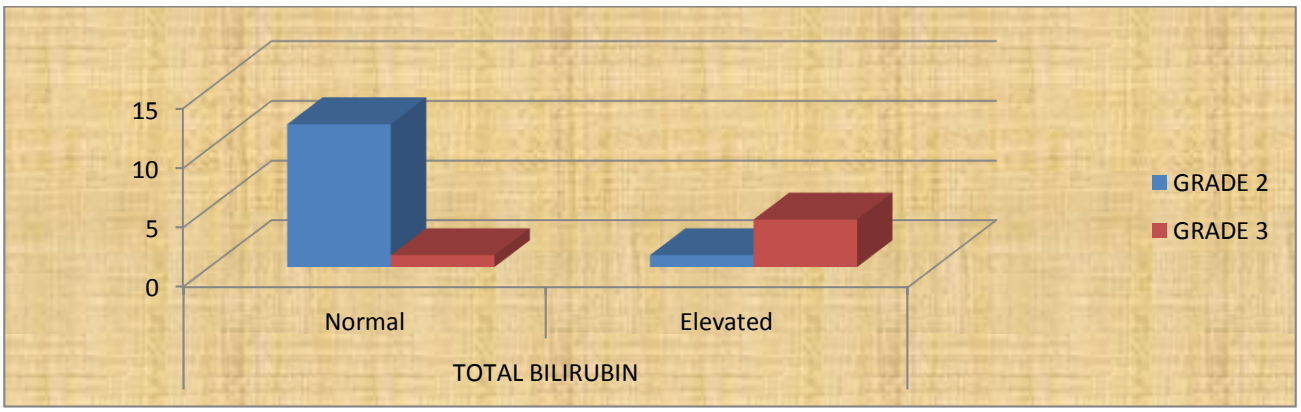
11) DIASTOLIC DYSFUNCTION GRADING VS LFT:

GRADE	LFT		P value
	Normal	Elevated	
2	12	1	0.001
3	0	5	
TOTAL	12	6	



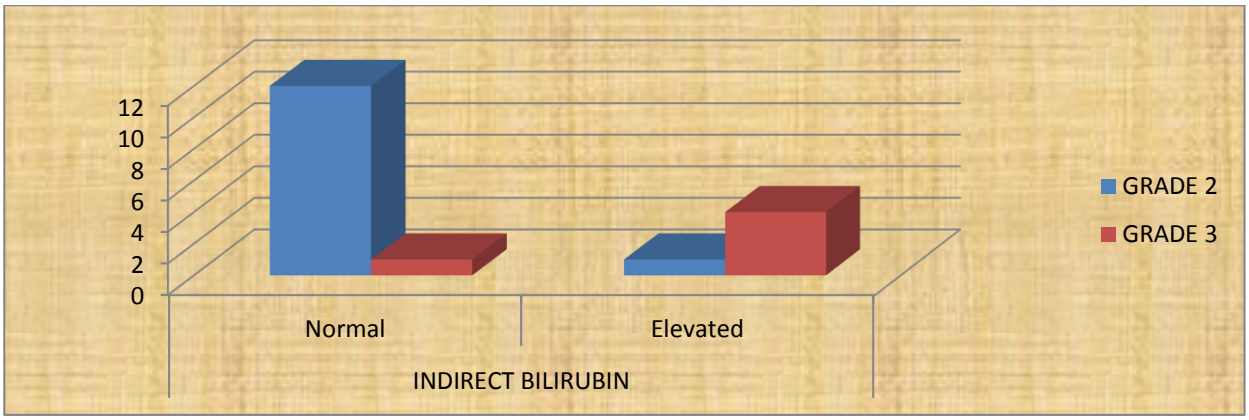
12) DIASTOLIC DYSFUNCTION VERSUS TOTAL BILIRUBIN:

GRADE	TOTAL BILIRUBIN		P value
	Normal	Elevated	
2	12	1	0.008
3	1	4	
TOTAL	13	5	



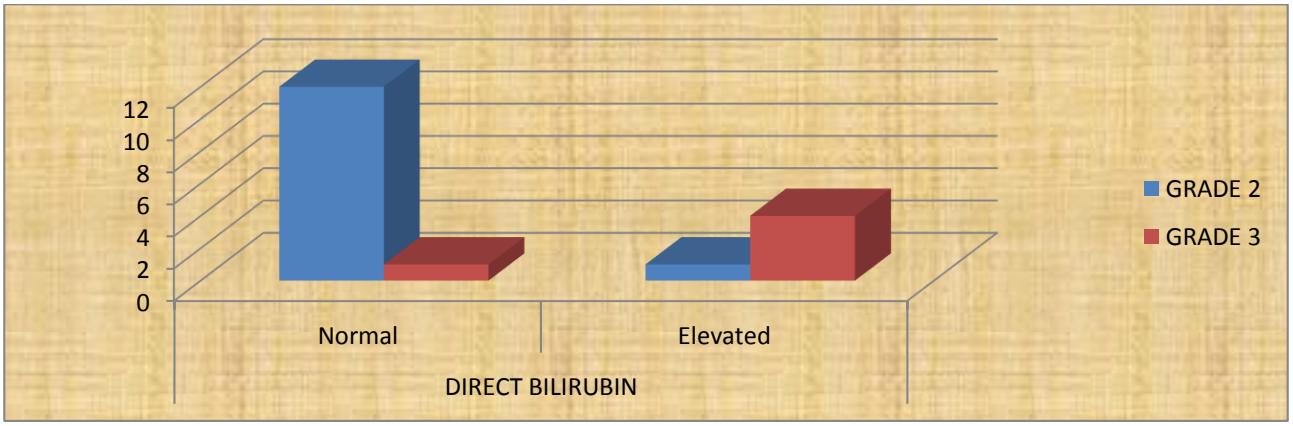
13) DIASTOLIC DYSFUCNCTION VS INDIRECT BILIRUBIN:

GRADE	INDIRECT BILIRUBIN		P value
	Normal	Elevated	
2	12	1	0.008
3	1	4	
TOTAL	13	5	



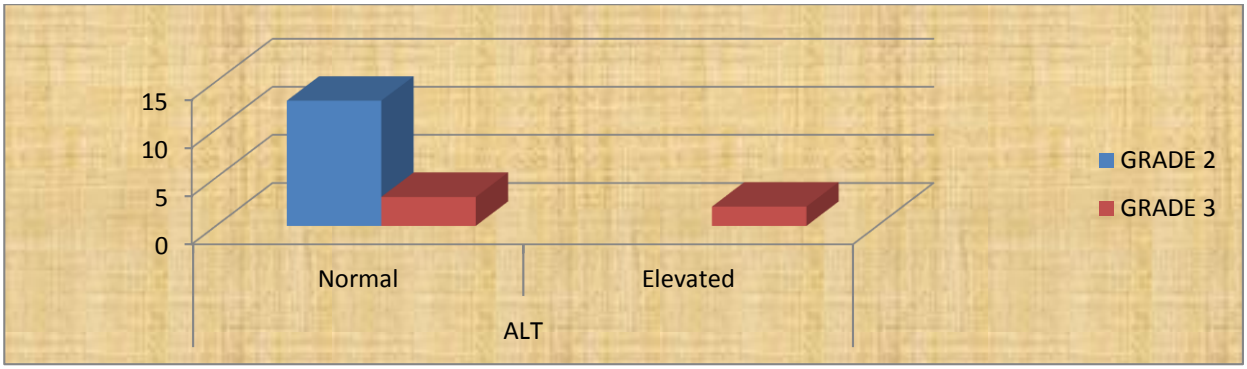
14) DIASTOLIC DYSFUNCTION VS DIRECT BILIRUBIN:

GRADE	DIRECT BILIRUBIN		P value
	Normal	Elevated	
2	12	1	0.008
3	1	4	
TOTAL	13	5	



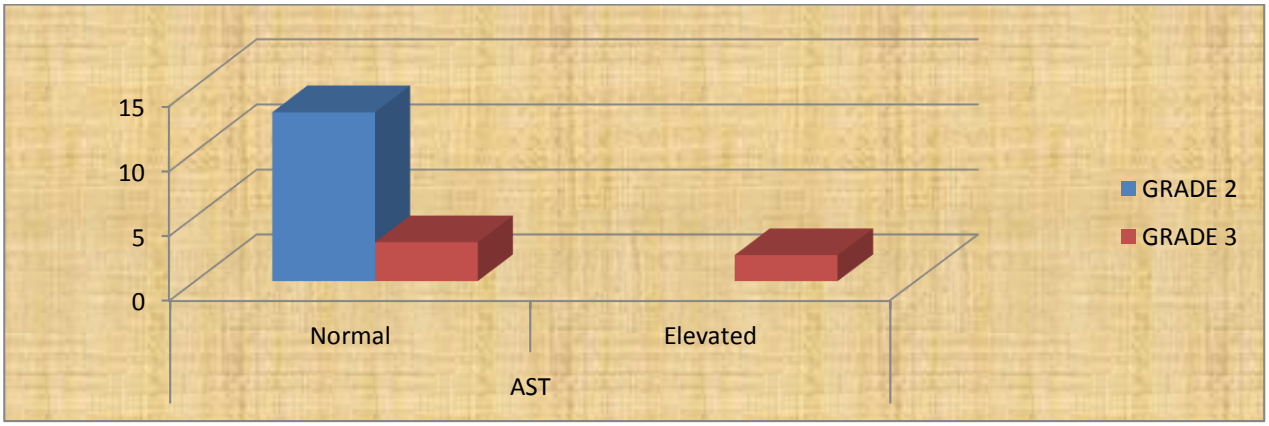
15) DIASTOLIC DYSFUNCTION VS ALT:

GRADE	ALT		P value
	Normal	Elevated	
2	13	0	0.065
3	3	2	
TOTAL	16	2	



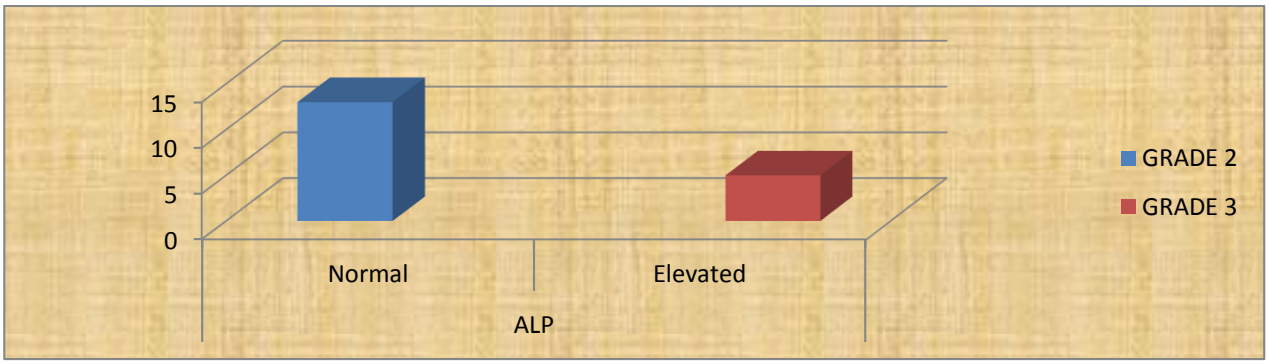
16) DIASTOLIC DYSFUCTION VS AST:

GRADE	AST		P value
	Normal	Elevated	
2	13	0	0.065
3	3	2	
TOTAL	16	2	



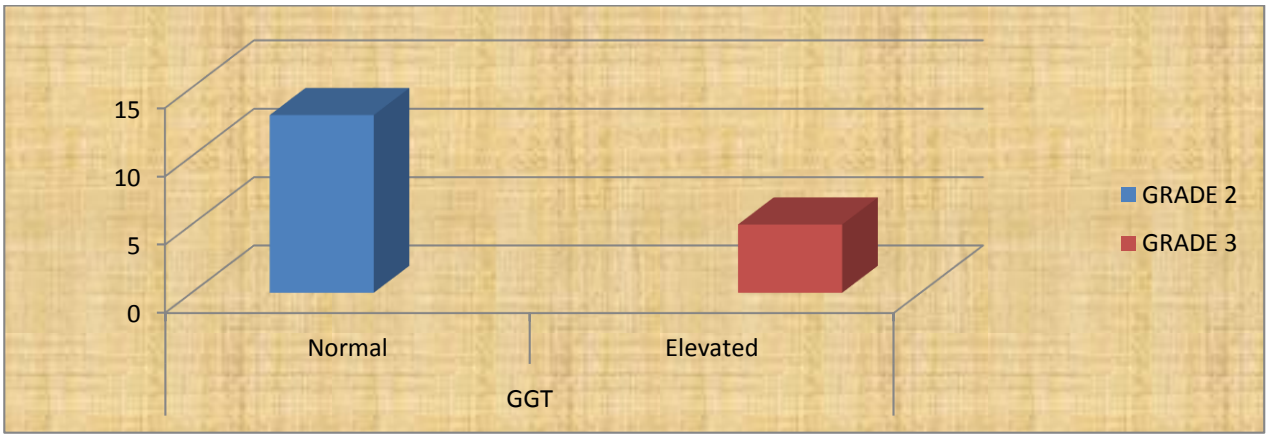
17) DIASTOLIC DYSFUNCTION VS ALKALINE PHOSPHATASE:

GRADE	ALP		P value
	Normal	Elevated	
2	13	0	<0.0001
3	0	5	
TOTAL	13	5	



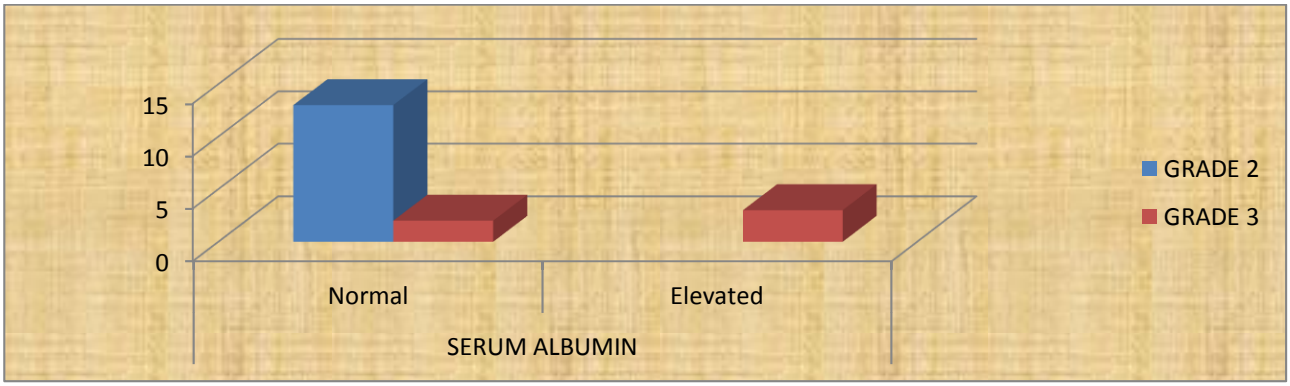
18) DIASTOLIC DYSFUNCTION VS GAMMA GLUTAMYL TRANSFERASE:

GRADE	GGT		P value
	Normal	Elevated	
2	13	0	<0.0001
3	0	5	
TOTAL	13	5	



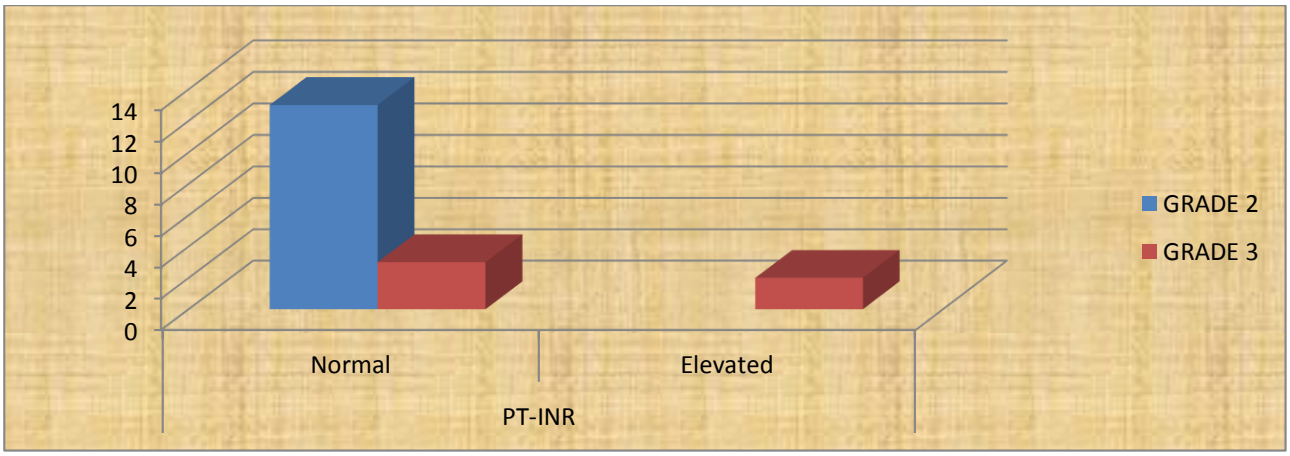
19) DIASTOLIC DYSFUNCTION VS SERUM ALBUMIN:

GRADE	SERUM ALBUMIN		P value
	Normal	Elevated	
2	13	0	0.012
3	2	3	
TOTAL	15	3	



20) DIASTOLIC DYSFUNCTION VS PROTHROMBIN TIME:

GRADE	PT-INR		P value
	Normal	Elevated	
2	13	0	0.065
3	3	2	
TOTAL	16	2	



DISCUSSION

Heart failure and liver dysfunction occurring as a result of that is of prognostic significance and there are various studies which have been proceeded to prove that point both in acute decompensated and chronic heart failure. The cardio-hepatic interactions that lead onto abnormalities in the liver function tests in setting of myocardial failure can be used as a corollary to understand and delineate the severity of heart failure ,thereby influencing the management aspect of the heart failure.

In this study, the study population was divided into two groups for sake of statistical analysis and disease pattern into: heart failure patient with reduced ejection fraction (HFrEF) and heart failure patient with preserved ejection fraction(HFpEF). The most common etiology of HFpEF was hypertensive heart disease while that of HFrEF was myocardial infarction followed by cardiomyopathies. Patients with myocarditis and valvular heart disease also presented with heart failure with reduced ejection fraction. One case of heat stroke also presented with severe myocardial depression with reduced ejection fraction. The general statistics showed that out of 50 patients, the patients with HFrEF were 32 and those with HFpEF were 18 in number. Although references suggest that the HFpEF is more prevalent nowadays , in this study period many number of patients with HFpEF had to be excluded since they were alcoholic and possibly they would have been in NYHA class 1 category not attending to the hospital settings in our region.

The mean age of in HFrEF was 58.9 years while that of HFpEF was 67.6 years signifying the aging factor which is factor in the pathogenesis of HFpEF . The standard deviation with in both groups differed significantly with greater deviation of 11.13 in HFrEF group showing younger age of onset of HFrEF. There were specific predominance in female patients in HFpEF group while the first group did not show significant difference. Maria et al study had patients with an average age group of 66 yrs with no major deviation noticed in patients with acute heart failure [(10)].

The HFrEF patients were divided according to the NYHA class and ejection fraction (EF) while the HFrEF were classified with help of NYHA class and also diastolic dysfunction grading which helped in correlating the severity of heart failure cases with the liver function abnormalities.

In HFrEF patients, out of total 32 there were 6 patients in class II, 11 patients in class III while 15 patients were in class IV heart failure. In HFpEF patients, out of 18 there were 13 patients in class II , 4 patients in class IV while a single patient presented with class IV heart failure symptoms. The prevalence of the abnormal LFT as a whole was present in 93 % of class IV, 83 % of class III failure while only 20 % of class II patients had LFT abnormalities showing increased prevalence among severe clinical grading. Szygula Jurkiewicz et al demonstrated elevated LFT values in NYHA class II/3 hypertensive patients was associated with higher mortality rates[(11)]. Shingawa et

al [12] also showed the association of prognostic significance of elevated LFT with increased morbidity of heart failure patients. In relation to ejection fraction compared with LFT, there was was excellent correlation with LFT abnormalities and decreasing ejection fraction with all 10 patients with less than 20% EF having elevated values while patients with 20-40% EF having 45 % of abnormal values.

The individual elevation of serum bilirubin in HFrEF group was 16% in NYHA class II, 45% in NYHA class III, 60% patient in NYHA class IV while 77 % of patients with ejection fraction <20% had 77 % elevation and patients with >20% having 34% elevation. All these abnormalities were mainly due to the relative elevation of unconjugated bilirubin values in proportion with conjugated bilirubin. Shinwaga et al showed higher (64%) prevalence of bilirubin abnormality compared to Lau et al(19%) [13] and CHARM trial [14].

In HFpEF patients, the prevalence of LFT abnormalities were only 6% in class II and it was around 80% in class III & IV pateints. The total prevalence of LFT abnormalities was 62.5 % indicating the prominence of LFT in heart failure. With diastolic dysfunction grading, grade 2 patients had less than 10 % while grade 3 patients all were having elevated LFT values. The elevation of serum bilirubin was 8% in NYHA class 1 while it was 80% in severe classes. The grade 2 diastolic dysfunction was associated

with the same with 8% in grade 2 and 80% in grade 3&4. This rise is proportionately more in the conjugated bilirubin than the unconjugated fraction revealing prevalence of cholestatic pattern in HFpEF patients rather than the unconjugated pattern in HFrEF patients. The rise in bilirubin has been associated as an important prognostic indication as well as severity indicator [14]. Single-center studies have shown higher mortality rates , cardiac transplantation, and HF rehospitalizations in

patients with increased plasma bilirubin .[16,17]

With respect to liver enzymes in the HFrEF patients , there was elevation in AST and ALT concomitantly with all patients with ejection fraction of <20% having elevated values and people with more than 20% ejection fraction having prevalence of only 30 %. Patients with NYHA class II had 20 %, class III had no elevation and class IV had 26 % elevation. This rise in enzymes can be attributed with to ischemic liver injury caused by hypoperfusion of liver. In HFpEF , the rise in liver enzymes were subdued with no elevation in class II patients while 2 out of 3 in class III developed transaminitis which was same with grade 2 and 3 diastolic dysfunction respectively indicating less of the hepatocyte damage with ejection fraction being preserved . Mattews et al [15]proved that AST along with serum bilirubin rise was independent marker of right ventricular failure

The enzymes relating to cholestasis such as ALT and GGT were only elevated in 15 % of patients with HFrEF, more so only in severely decompensated patients like class III & 4 failure and ejection fraction of less than 20%. In patients with HFpEF, the elevation was present in one third of the patient studied implicating the prevalence of cholestatic pattern more in cases of heart failure with preserved ejection fraction. Richman et al [19] proved this cholestatic pattern may be due to congestive hepatopathy in HFpEF leading onto increased hepatic venous pressure causing intrahepatic small biliary radicles obstruction and also bile thrombi [15]. Poelzl et al. [17] proved that serum GGT signifies independently prognostic information for established clinical and biochemical markers , ischemic etiology, NYHA functional class, and hear failure markers such as N-terminal pro–B-type natriuretic peptide. Ruttmann et al. [18] showed that GGT to be a prognostic indicator of death including all cause mortality,incident heart failure indicating that GGT shows promise as a marker for subclinical or early stage disease.

With respect to the serum albumin , hypoalbunemia was present in 40 % of HFrEF group with the 16 % in NYHA class II and 73 % of class IV patients. With relation to ejection fraction , the lower (EF<20%) group had nearly 100 % hypoalbuminnemia while only 17 % had in group with higher ejection fraction. In patients with HFpEF , there was reduction only with 60% of NYHA class III patients and grade 3 diastolic dysfunction patients . The reduction has been attributed to the nutritional status [20,21] with other factors

such as hemodilution [22] and inflammation playing their own part [23]. Horwich et al. [23] demonstrated that hypoalbuminemia greatly increased the all-cause mortality, progressive heart failure , and increased risk of transplantation in a set of patients with NYHA class III/IV symptoms. Low albumin levels also have been found to have prognostic value in patients with acute decompensated HF after adjustment for multiple prognostic variables, including N-terminal pro–B-type natriuretic peptide .[24,25]

Patients with HFrEF showed elevation in Prothrombin time in 45 % of only NYHA class IV patients and 50% in lower (<20%) ejection fraction group and only 17% in higher (EF >20%) group. In the HFpEF group, only 2 patients showed elevation of Prothrombin time only with NYHA class III&IV and diastolic grading 3. Furman et al (26)showed that the increase in the PT-INR >2 signifies risk of death in greater number of cohorts while Raurich et al(27) confirmed the same . In our study also there was 100 % mortality with patients in league of elevated PT-INR in the HFrEF group.

Hence the alterations in liver functions are proved beyond doubt in this study also linking it to the clinical and echocardiographic assessment where the alterations are more pronounced with increasing severity and functional class.

SUMMARY

1) In HFrEF group, the prevalence of LFT abnormalities was 63% while in the in HFpEF group the prevalence was 33%.

2) HFrEF group presented with hepatocellular pattern of bilirubin elevation with more unconjugated bilirubin, transminases while the HFpEF group presented with cholestatic pattern of elevation enzymes like GGT and ALP.

3) Functional NYHA class with greater severity (class III and IV) were associated with abnormal LFT values and provided an increasing trend with increasing severity in terms of absolute values of LFT .

4) Echocardiogram assessment correlated well with the severity of heart failure in terms of both HFrEF and HFpEF patients.

5) Coronary artery disease is the leading cause in HFrEF group while hypertensive heart disease led in HFpEF group.

CONCLUSION

The effect of heart failure on hepatic functions and the cardio hepatic interactions that occur in the full spectrum of heart failure needs greater elucidation not only for the management of heart failure and its associated complications but also to assess the prognosis, need for urgent surgical intervention, the need for ventricular assist devices .This study on prevalence of LFT abnormalities and its correlation with functional , echocardiological severity may be of help in assessing the heart failure patients even in primary health care setting and lead onto better management of the heart failure patients.

LIMITATIONS OF THE STUDY

1) The sample size is small.

2) There was no division of acute and chronic heart failure.

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PROFORMA

Name: D.O.A:-

Age/sex: D.O.D:-

Hospital no: Phone No:

Occupation:

Address:

History:

Chest pain			Pedal edema		
Dyspnoea			Dilated neck veins		
Palpitations			Abdominal distension		
Syncope			dyspepsia		
Orthopnoea/PND			Bleeding diathesis		
Jaundice			Bowel disturbances		

Past history:

H/o liver diseases

H/o drug intake(ATT)

Personal history;

smoker- yes/ no alcoholic –yes /no

General examination:

Pallor Icterus Cyanosis Clubbing Lymphadenopathy Oedema

PULSE : BP : / mm Hg JVP:

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM

RESPIRATORY SYSTEM

GASTRO INTESTINAL SYSTEM

CNS

INVESTIGATIONS:

CBC: Urine Sugar ULTRASOUND

TC Albumin

DC Deposits

Hb RFT: Urea Creatinine

Platelets Na- K

ESR

LIVER FUNCTION

Tot.bil	Direct	indirect	SGOT	SGPT	ALP	TOT.PROT	ALB	GLOB	PT	APTT

ECG:

CHEST XRAY:

ECHO:

MASTER CHART

HEART FAILURE WITH REDUCED EJECTION FRACTION															
S.NO	NAME	AGE	SEX	DIAGNOSIS	TOT.BIL	UNC.BIL	CON.BIL	ALT	AST	GGT	ALP	SR.ALB	PT(INR)	EJ.FRAC	CLASS
1	Amalan	62	M	MI	3.6	2.2	1.4	786	712	68	58	4	0.9	28	C
2	Vijayan	68	M	MI	2.8	2.2	0.6	680	595	62	42	2.8	0.8	18	D
3	Mythili	56	F	MI	0.9	0.7	0.2	48	39	75	46	3.7	1.1	34	B
4	Yuvan	40	M	MI	1	0.7	0.3	52	45	52	60	3.6	1	36	B
5	Thamarai	52	F	MI	1	0.8	0.2	586	554	65	64	2.2	1	18	D
6	Seeniappan	68	M	MI	4	3.2	0.8	752	702	45	48	2.4	1.5	24	D
7	Duratchi	60	F	MI	0.8	0.6	0.2	52	48	48	54	3.7	0.8	30	B
8	Senthai velan	65	M	MI	0.9	0.8	0.1	50	28	56	50	3.8	0.9	27	C
9	Ramani	67	F	MI	3.2	2.4	0.8	1086	992	75	68	3	1.1	18	D
10	Anthony	59	M	MI	1.1	0.8	0.3	48	44	45	72	3.9	1	32	D
11	Shahila	55	F	HEAT STROKE	4.2	3.4	0.8	44	42	454	414	2	1.1	38	B
12	Meena	65	F	VALVULAR HEART DISESASE	2.9	1.8	1.1	546	512	79	54	3.1	1.3	20	D
13	Anban	42	M	MYOCARDITIS	1	0.8	0.2	486	452	48	50	2.8	1	25	D
14	Jeyaseelan	38	M	MYOCARDITIS	0.9	0.7	0.2	42	38	56	52	4.1	0.9	26	C
15	Mohana	55	F	CAD	0.8	0.6	0.2	596	498	64	68	2.4	0.9	23	D
16	Rasathi	65	F	CAD	0.9	0.7	0.2	492	452	512	466	2.5	1.7	18	D
17	Saraswathy	67	F	CAD	2.2	1.8	0.4	58	54	65	72	4.2	0.8	27	C
18	Gopal	70	M	CAD	5	3.2	1.8	1076	984	452	586	2.2	1.4	18	D
19	Trace meena	64	F	CAD	1.1	0.9	0.2	62	58	56	44	4.2	0.9	32	C
20	Papathi	74	F	CAD	4	3.5	0.5	986	812	57	40	2.1	1	15	C
21	Nivin mark	59	M	CAD	1	0.9	0.1	60	48	46	56	4.2	1	38	B
22	Thirupathi	75	M	CAD	1	0.8	0.2	412	404	72	80	3.8	1.6	24	D
23	Chandran	65	M	CAD	3.9	3	0.9	816	784	56	54	2.4	1	20	D
24	Pandiammal	66	F	CAD	0.9	0.7	0.2	44	48	49	56	3.9	0.9	34	B
25	Seeniammal	62	F	CAD	0.8	0.6	0.2	25	32	66	48	3.9	0.9	36	C
26	Latha	60	F	CAD	0.8	0.6	0.2	46	45	64	52	4	0.8	28	C
27	Jayanthan	63	M	CAD	1	0.8	0.2	48	44	48	56	4.1	0.9	30	C
28	Gurusamy	76	M	CAD	3.8	3	0.8	986	884	44	68	4.2	1.4	26	D
29	Mannan	45	M	VALVULAR HEART DISESASE	2.4	2	0.4	54	48	50	52	4.3	1	28	C
30	Kokila	40	F	VALVULAR HEART DISESASE	2.6	1.8	0.6	786	612	512	566	2.5	0.9	16	D
31	Christie sheela	38	F	VALVULAR HEART DISESASE	2.2	1.8	0.4	52	48	65	52	3.6	0.9	32	C
32	Anbumathi	44	F	VALVULAR HEART DISESASE	3.5	2.8	0.7	1086	912	408	526	3.7	1.3	24	D

HEART FAILURE WITH PRESERVED FRACTION

S.NO	NAME	AGE	SEX	DIAGNOSIS	TOT.BIL	UNCON	CONJ	ALT	AST	ALP	GGT	SR.ALB	PT INR	DIASDYSGR	CLASS
1	Selvi	66	F	HTN/CAD	1.1	0.9	0.2	48	52	82	44	3.5	1	2	B
2	Meena	75	F	HTN/CAD	1	0.8	0.2	45	52	45	48	3.6	1	2	B
3	Urval	72	F	HTN/CAD	2.8	1.5	1.3	52	62	542	486	3	0.9	3	C
4	Nangai	68	F	HTN/CAD	0.9	0.7	0.2	70	68	46	72	4.4	1	2	B
5	Esakki	59	F	HTN/CAD	3.6	1.9	1.7	584	514	414	454	2.7	1.5	3	C
6	Muneeswaran	56	M	OBESITY	0.8	0.6	0.2	48	70	55	80	3.7	1.2	2	B
7	Mariammal	67	F	HTN/CAD	1	0.9	0.1	40	34	65	68	3.6	1.1	2	B
8	Maayan	80	M	HTN/CAD	3.2	2	1.2	102	114	482	386	3.6	1	3	C
9	Nambirajan	65	M	HTN/CAD	1	0.9	0.1	64	60	72	81	3.5	0.9	2	B
10	Yasodhai	71	F	HTN/CAD	1	0.8	0.2	58	48	80	56	3.8	1	2	B
11	Guruvammal	66	F	HTN/CAD	1.1	0.9	0.2	62	58	55	48	3.6	1	2	B
12	Rasiammal	80	F	HTN/CAD	0.9	0.6	0.3	64	52	66	66	3.7	0.8	2	B
13	Balan	76	M	HTN/CAD	3.2	2	1.2	414	385	494	478	4	1.1	3	D
14	Rakku	69	F	HTN/CAD	0.9	0.7	0.2	7	80	56	46	3.5	0.9	2	B
15	Sembaruthi	66	F	HTN/CAD	0.8	0.6	0.2	48	40	512	554	2.9	1.6	3	C
16	Vijaya	68	F	HTN/CAD	1	0.8	0.2	36	38	74	34	3.5	0.9	2	B
17	Lallita	54	F	CONS,PERI	3	1.8	1.2	61	65	80	76	3.6	1.1	2	B
18	Murugan	60	M	HTN/CAD	1.1	0.8	0.3	73	58	48	56	4	1	2	B

KEY TO MASTER CHART

1) S.NO – SERIAL NUMBER

2)TOT.BIL – TOTAL BILIRUBIN

3)UNC.BIL – UNCONJUGATED BILIRUBIN

4)CON.BIL – CONJUGATED BILIRUBIN

5)AST – ASPARTATE TRANSAMINASE

6)ALT- ALANINE TRANSAMINASE

7)GGT - GAMMA GLUTAMYL TRANSFERASE

8)ALP- AKALINE PHOSHATASE

9) EJ.FR- EJECTION FRACTION

10) CLASS- NYHA HEART FAILURE CLASSIFICATION

11)DIA.DYS- DIASTOLIC DYSFUNCTION GRADING

ABBREVIATIONS

1) HF – Heart Failure

2) HFrEF – Heart Failure with reduced ejection fraction

3)HFpEF – Heart Failure with preserved ejection fraction

4) AST – Aspartate Transaminase

5) ALT – Alanine Transaminase

6)GGT – Gamma Glutamyl Transferase

7)ALP –Alkaline Phosphatase

8) PT-INR – Prothrombin Time International Normalized Ratio

9)RAAS –Renin Angiotensin Aldosterone System

10) AT –Angiotensin

11)ACEI –Angiotensin Converting Enzyme Inhibitor

12)ET – Endothelin

13)AVP –Arginine Vasopressin

14)NYHA – New York Heart Association

CONSENT FORM

நோயாளிகளுக்கு அறிவிப்பு மற்றும் ஒப்புதல் படிவம்
மருத்துவ ஆய்வில் பங்கேற்பதற்கு

ஆய்வு செய்யப்படும் தலைப்பு :
பங்கு பெறுபவரின் பெயர் :
பங்கு பெறுபவரின் வயது :

		பங்கு பெறுவர் இதனை ✓ குறிக்கவும்
1	நான் மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் நான் படித்து புரிந்து கொண்டேன். என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டுள்ளது என அறிந்து கொண்டேன்	☐
2	நான் இவ்வாய்வில் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும், எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன்.	☐
3	இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன்.	☐
4	இந்த ஆய்வில் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.	☐
5	இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன், ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ, அல்லது எதிர்பாராத, வழக்கத்திற்கு மாறான நோய்குறி தென்பட்டாலோ உடனே இதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன்.	☐

பங்கேற்பவரின் கையொப்பம் / ..... இடம்.....தேதி.....
கட்டைவிரல் ரேகை
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மையம் .....
கல்வியறிவு இல்லாதவற்கு (கைரேகை வைத்தவர்களுக்கு) இது அவசியம் தேவை
சாட்சியின் கையொப்பம் / ..... இடம் ..... தேதி .....
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